The endoluminal bypass for occlusive lesions of the superficial femoral artery

Lensvelt, Martha Maria Antonia

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of the superficial femoral artery

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Stellingen behorend bij proefschrift

'The endoluminal bypass for occlusive lesions of the supericial femoral artery'

1. De endoluminale bypass is een veilige behandelmodaliteit voor uitgebreid stenoserend vaatlijden in het traject van de arteria femoralis superficialis, met patencies die vergelijkbaar zijn met die van chirurgische bypasses. *Dit proefschrift*

2. Het gebruik van een gecoverde stent leidt niet tot klinische achteruitgang na falen van de stentgraft, ondanks het overstenten van collateralen. *Dit proefschrift*

3. De endoluminale bypass is ook als secundaire procedure na een gefaalde chirurgische bypass een goede optie. *Dit proefschrift*

4. Het plaatsen van een endoluminale bypass is een eenvoudige techniek, waarbij de re-entry met een retrograde body floss techniek een goedkoop alternatief is voor re-entry devices. *Dit proefschrift*

5. Walking is man's best medicine. *Hippocrates*

6. There are, it has been said, two types of people in the world. There are those who, presented with a glass of water that is exactly half full, say: this glass is half full. And then there are those who say: this glass is half empty. The world belongs however to those who can look at the glass and say: what's up with this glass? Excuse me? This is my glass? I don't think so. My glass was full! And it was a bigger glass! *Terry Pratchett, The Truth*

7. Balnea vina venus corrumpunt corpora nostra, sed vitam faciunt balnea vina venus. *Onbekend*

8. A fall from the third floor hurts as much as a fall from the hundredth. If I fall, may it be from a high place. *Paulo Coehlo*

9. Vrouwen in de chirurgie: 'Look like a girl, act like a lady, think like a man.' *Caroline K. Simon*

10. Druk ben je in je hoofd. *Lensvelt zelf*

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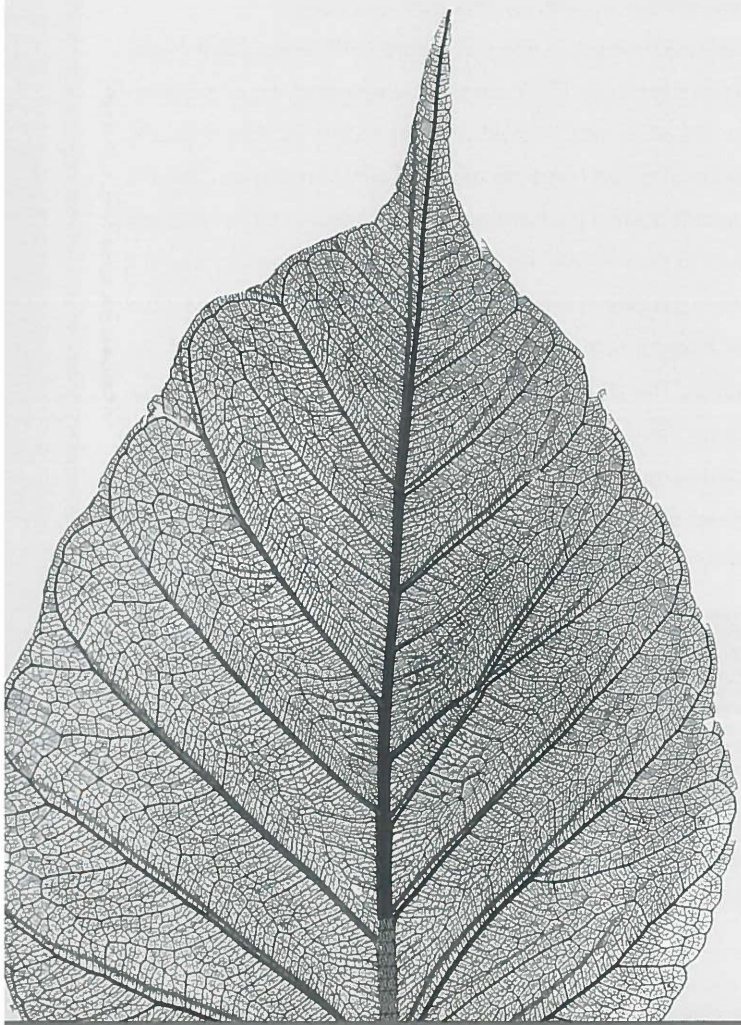
General Introduction



General Introduction

A brief history of femoropopliteal bypass surgery

Peripheral bypass surgery is a relatively young section of vascular surgery. Although atherosclerotic lesions were present in Egyptian mummies dating back 3500 years ago, we have long lacked the techniques to adequately treat occlusive arterial disease. Aneurysmal disease of the popliteal artery on the other hand has been treated since Antyllus (200AD) by applying ligatures to the entering and exiting arteries of the aneurysm and packing the cavity. This technique did not change until John Hunter (1728-1793) redesigned it by ligating the superficial femoral artery at Hunter's canal. This technique would remain again until Rudolph Matas developed the endoaneurysmorraphy in 1888[1].

Arterial reconstruction developed much slower. It was not before 1891 when Jassinowsky reported success in the suturing of arteries. In 1896 Jaboulay developed the end-to-end anastomosis in a carotid artery. His work was refined and expanded by Alexis Carrel. Carrel emphasized the importance of tissue handling and fine suture materials. Trauma to the intima was meticulously avoided when performing the anastomosis as he believed damage to the intima would lead to thrombosis. Arterial blood flow restoration was still not considered the main solution to peripheral arterial disease. In 1909 Leriche attempted to bypass a thrombosed artery using a vein graft, but failed as the distal limit of the thrombosis could not be identified. The discovery of X-rays in 1896 and consequential development of arteriographies by Barney Brooks in 1923 was an important step in the development of peripheral bypass surgery. Contemporaneously Jay McClean developed heparin (1916), which was successfully used in experimental arterial surgery afterwards. These discoveries led to an increase in popularity of the endarterectomy as performed by Jao Cid dos Santos in 1936. Unfortunately, the endarterectomy did not provide a full solution for longer occlusion of the SFA[2].

Figure 1. Rene Leriche with his students, including Mikael DeBakey, Rene Fontaine, Jean Cid dos Santos and Jean Kunlin.

It was not until 1948 that the first femoral artery bypass was created. Jean Kunlin (Fig. 1) performed an autologous venous femoral bypass on a 54-year old man with gangrene of the foot.

The wounds healed postoperatively although the patient died a year after from massive stroke. The autologous venous surgical bypass has been the gold standard for long occlusion of the SFA ever since.

Without a vein ...

Autologous venous femoral bypasses remain the gold standard as their long-term patency rates exceed those of other bypasses. Primary patency rates of 75% at 5 years are yet to be attained by prosthetic bypasses. Unfortunately almost a third of the patients eligible for femoropopliteal bypass surgery do not have a suitable vein[3], which makes the use of prosthetic materials necessary. Preservation of the autologous saphenous vein for future bypass surgery, for example for coronary bypass surgery, is deemed obsolete[4].
Several prosthetic bypasses (polytetrafluorethyleen (PTFE), Dacron) and allografts (human umbilical vein (HUV)) have been developed during the last decades.
HUV would, in theory, improve patency rates as it consisted of venous material. In below knee (BK) bypass surgery it improved primary patency compared to PTFE, but with a high incidence of graft dilatation (30%[5]). More recent studies do not endorse these results, but HUV is no longer available and taken off the commercial market because of transferable viral issues[6].
Dacron and PTFE have comparable primary and secondary patency rates[7,8]. Still in both above-knee (AK) as well as BK bypasses autologous vein conduits have significantly higher patency rates compared to PTFE[9]. The use of a vein cuff in a synthetic bypass does not seem to improve patency rates in AK bypasses.
Recently, heparin-bonding of prosthetic bypasses has been introduced. This technique improved mid-term patency rates in both Dacron grafts (47% vs 35% 3-years primary patency[10]) and PTFE grafts (80% 2-year primary patency[11,12]). Limb salvage rates were also significantly improved (86% vs 74%). The Propaten trial compared Hb-PTFE grafts with standard PTFE grafts and reported primary patency rates of 87% and 80%, respectively. This difference was greatest in the femoropopliteal bypasses[12]. With heparin-bonding synthetic PTFE and Dacron grafts have improved patency rates comparable to autologous venous conduits.
Surgical bypasses are associated with a high complication rate (5-100%[13,14]) and a prolonged hospital stay (average of 5 days[15]). The frail vascular population might benefit from a less invasive treatment strategy. Since 1994 the remote superficial femoral artery

endarterectomy (RSFAE) is a minimal invasive alternative for the surgical bypass. It avoids synthetic materials and has a minimal invasive character as it is performed through a groin incision. In the REVAS trial (Remote Endarterectomy Versus Supragenicular femoropopliteal bypass) primary patency rates at three years were 47%[16]. This is comparable to the synthetic grafts (56%), but inferior to the venous grafts (65%). The main confounding factor is early in-stent stenosis due to neointima hyperplasia (80% at 1-year[16]).

Endovascular treatment

Over the past five decades interventional radiology has contributed a great deal to the treatment modalities of peripheral vascular disease. After Sven-Ivar Seldinger developed a safe method of puncturing the arteries in 1953[2], developments followed rapidly. In 1964 Charles Dotter (Fig. 2) performed the first angioplasty on an 82-year old woman with gangrene of the foot. She fully recovered[17]. These new minimal invasive techniques have conquered a place among the treatment modalities of peripheral arterial disease. In 2007 the Trans Atlantic interSociety Consensus (TASC II) recommended balloon angioplasty with or without stent placement of short lesions of the superficial femoral artery (SFA) (TASC II A and TASC II B lesions[18]). In longer, more complex lesions (>15cm) however, venous surgical bypass remained the gold standard.

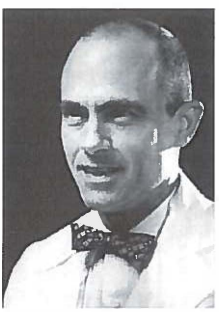


Figure 2.
Charles Dotter

For longer lesions (mean 8 cm) primary patency rates following PTA of the SFA are reported to be as low as 33%-55% at 1-year follow-up[19,20]. When comparing PTA of the SFA with optimal medical treatment, PTA shows better short term results (<6 months) but a 2-years followup both groups are comparable[21], especially for longer lesions.

The main limitation for PTA is the occurrence of restenosis due to neointimal hyperplasia. Drug eluting balloons (DEB) reduce this hyperplasia on the short term in the Thunder and FemPac trials (significant reduction of lumen loss at 6 months)[22,23].

To reduce restenosis nitinol stent placement has been introduced. Early results of studies comparing PTA to PTA with stent placement show no significant difference in the overall primary patency rates, 36% vs 41%[24], but in longer lesions patency rates do improve significantly (12% vs 34%, $p<0.05$). The three major randomized trials are the

FAST, VIENNA and RESILIENT trials[25-27]. The FAST trial randomized 244 patients and their target lesion revascularisation rate (TLR) is higher in the PTA alone group (18% vs 15%). The RESILIENT trial report significant superior patency rates at 1 year for PTA with stent placement in short lesions (81% vs 36%, P<0.0001) in a population of 204 patients. Finally the VIENNA trial is the smallest of the three (N=104), but they reported significantly lower restenosis rates after stenting. These studies show that use of stents increases patency rates after PTA.

A further development of stents is the introduction of covered stents. The mechanical barrier of the cover prevents in-stent restenosis, reducing restenosis rates to edge stenosis only, as described recently by Fritschy et al[28]. From 2000 several studies have shown primary patency rates between 74% and 83% at 12-months follow-up after treatment of long SFA lesions (mean length 22cm, range 4-40cm)[29-32]. These results are comparable to synthetic surgical bypasses. Results are depended on device diameter, with smaller diameters (5mm) yielding poorer results (P=0.001).

A randomized controlled trial comparing endografts with open surgical PTFE AK bypass[33,34] confirms these results in long lesions of the SFA (26cm, +/-15cm), describing comparable patency rates at 4 year follow up (59% and 58%, respectively). Secondary patency rates are 74% for the endograft group and 71% for the surgical bypass group. Both show no significant difference.

To further improve endograft patency rates and reduce edge stenosis drug-eluting and/or drug-bonded stents have been developed. The advantage of these stents is the effect on neointimal hyperplasia and cell proliferation[35]. For paclitaxel-eluting stent grafts one-year primary patency is as high as 86% for long lesions of the SFA[36].

Recently heparin-bonding has been integrated with a PTFE covered stent (Viabahn). This might increase patency rates of this endograft even further, as heparin-bonding has increased patency rates of synthetic surgical bypasses[12,36].

Aim and outline of this thesis

In this thesis we try to describe and clarify the place of endoluminal stentgrafts in the treatment algorithm for chronic long occlusive disease of the SFA by answering specific questions.

- What are the current treatment modalities and how do endografts fit in this algorithm (Ch2, Ch8)?
- What are the patency rates of heparin bonded endografts for long lesions of the AFS (Ch3)?
- How can we further improve patency rates of endografts (Ch3)?
- How can we improve technical success rates for endograft placement (Ch7)?
- What is the outcome of patients after failure of the endograft (Ch5 & Ch6)?
- Does the overstenting of collaterals worsen patient clinical outcome after endograft failure (Ch5)?

Finally we have started a prospective randomized controlled trial comparing heparin-bonded endografts with autologous venous surgical bypasses (SUPERB trial). The study protocol for this still including trial is described in Chapter 8.

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Chapter 2

strategies for extensive chronic SFA occlusions: indications and results

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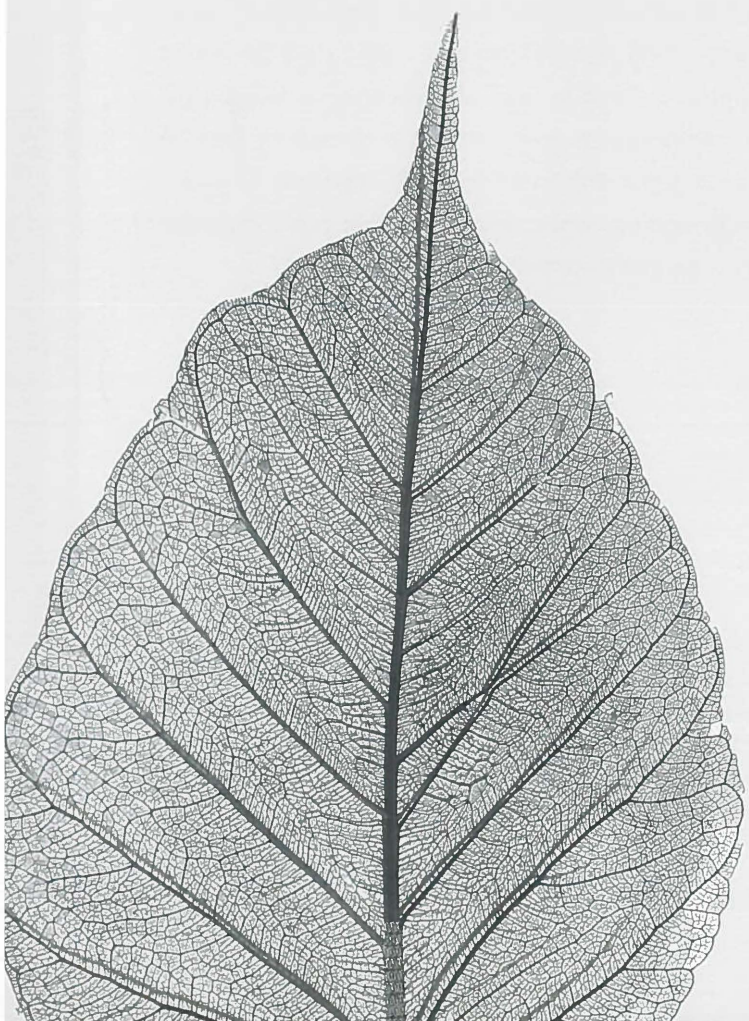

J Cardiovasc Surg (Torino) 2012; 53 (1 Supl 1): 161-170

Summary

Treatment modalities for extensive chronic occlusive disease of the superficial femoral artery (SFA) have changed during the last decades. In this chapter we provide an overview of current treatment modalities for extensive chronic occlusive disease of the SFA. Although the autologous venous conduit is still considered the gold standard for treatment of long occlusive SFA lesions, endoluminal therapy is gaining territory. Its minimal invasive character has great advantages in the frail vascular patient population. Percutaneous transluminal angioplasty is first choice in short SFA lesions, but patency rates decrease with longer lesions. When percutaneous transluminal angioplasty is combined with nitinol stent placement patency rates significantly improve. Patency rates of percutaneous transluminal angioplasty combined with covered stents are within reach of patency rates of prosthetic surgical bypasses. Drug-bonding in surgical PTFE bypasses increased patency rates significantly. In the near future drug-eluting and drug-bonded devices might further increase results of endovascular treatment.

Introduction

Epidemiology

Peripheral arterial disease (PAD) is a worldwide problem with a prevalence in the general population of 12-14%, affecting up to 20% of those persons over 70 years of age. The incidence of PAD increases with age from approximately 0.3% per year for men between 40-55 years of age, to 1% in men older than 75 years[1]. The risk factors for PAD are similar to those for coronary heart disease, and include smoking, diabetes mellitus (DM), hypertension, dyslipidemia and obesity. DM and smoking are particularly strong risk factors for the development of PAD. Smoking increases the risk of critical limb ischemia (CLI) 2.3 times compared to subjects who never smoked, while DM confers a 4.4 times increased risk of developing CLI compared to the general population[2]. PAD is a marker for systemic atherosclerotic disease. Persons with PAD, compared to those without, have four to five times the risk of dying of a cardiovascular event, resulting in a two to three times higher total mortality risk[3].

Critical limb ischemia represents the extreme of this condition and may culminate to tissue loss, sometimes requiring amputation of the affected limb. The prevalence of CLI in the general population is scarce. An European cross-sectional study estimated the prevalence to be 2,500 per million inhabitants[4]. This prevalence, however, is higher in the elderly population (age > 75 years). The progression of PAD to CLI varies considerably in the published literature. One of the largest populations studied by Acquino et al followed 1244 patients with intermittent claudication (IC) during 45 months. The authors combined the rate of developing an ischemic ulcer (23% over 10 years) with the rate of developing ischemic rest pain (30% over 20 years), which led to an annual rate of 5.3% of claudicants progressing to CLI[5]. Patients with IC and/or CLI are known to have a low health-related quality of life (HRQOL). Their HRQOL is comparable to patients with cardiac disease or stroke. Besides diminished quality of life for individual patients, PAD also has a great impact on health care from a societal perspective. Few published data are available on the health care costs. An American study estimated the annual PAD-related costs from an administrative claims database. They found total mean annual PAD-related costs around $6000 per patient per year (PPPY). Hospitalizations account for the largest part with 75% of the total annual PAD-related costs per PAD patient. PAD-related non-coronary procedures average $729 PPPY (12.2% of total annual PAD-related costs), and

PAD-related medications (including antihypertensive and lipid-lowering therapy) total $610 (10.2% of total annual costs)[6]. Obviously, these results may differ between hospitals and regions.

Classification

In 2000 the Trans-Atlantic InterSociety Consensus developed guidelines to provide an international consensus on the diagnosis and treatment of PAD (Trans-Atlantic Inter-Society Consensus, TASC). With the development of new and improved treatment modalities the TASC workgroup updated their recommendations and revised the TASC I morphological stratification and treatment options in 2007[7]. For the classification of femoropopliteal lesions the TASC II guideline extended the possibilities for endovascular treatment modalities. TASC II A lesions are short occlusions (<5cm) or stenoses (<10cm) optimally treated with percutaneous transluminal angioplasty (PTA). TASC II B lesions consist of multiple short stenoses (<5cm) or single long stenosis (<15cm). These lesions are also optimally treated by PTA. TASC II C lesions are classified as multiple occlusions and/or stenoses totaling >15cm in length. The TASC guideline recommends that these lesions are treated with surgical bypass. Endovascular modalities can be considered as secondary treatment after surgical intervention.

TASC II D lesions are extensive (>20cm) chronic occlusions of the superficial femoral artery (SFA). Surgical bypass is recommended for this type of lesions. Recent developments of endovascular modalities have expanded treatment options for TASC II D lesions. Treatment strategies for these lesions are summarized in this chapter.

Treatment modalities

Conservative treatment

Conservative treatment of PAD consists of lifestyle changing treatment (exercise and risk factor reduction) and optimal medical treatment. These regimes are the first line treatment in patients with extensive SFA disease without limb threatening symptoms, who are considered fit for exercise. Optimal medical treatment is recommended as a supplement for all patients independent of their symptoms at presentation.

Lifestyle changing treatment

Although intermittent claudication is often the first symptom of systemic atherosclerotic disease and this population provides a potential opportunity for secondary prevention, life changing programs are not common practice in this population. The reduction of cardiovascular risk factors reduces morbidity and mortality due to coronary and cerebrovascular events, but also decreases the progression of peripheral atherosclerotic disease. Smoking cessation is the most clinically effective intervention for patients with atherosclerosis[8]. Smokers with PAD have higher major amputation rate than non-smokers (6% vs 0%) and are more likely to undergo vascular reconstructions. Patients who quit smoking also showed a 36% relative risk (RR) reduction for all-cause mortality[9] and a two-fold increase of their 5-year survival rate[10]. Special programs and patient motivation help successful smoking cessation.

Exercise therapy can benefit patients with IC[11]. Several theories exist about the underlying mechanisms. Exercise may improve the use of oxygen in the limb, reduce reliance on anaerobic metabolism, increase distribution of blood flow to the limb and decrease the viscosity of the blood[11-13]. A recent Cochrane review demonstrated that an exercise program was beneficial for patients with IC compared to non-exercised control groups[14]. Exercise significantly improved maximum walking distance, pain free walking distance and maximum walking time. No improvement was seen in ankle brachial index (ABI). Supervised walking training improved the walking distance more than unsupervised exercise therapy[15].

Further risk factor reduction includes lipid lowering therapy and weight loss. Lipid lowering therapy through dietary measures offers only a small cardiovascular benefit. Statin treatment is discussed in the next chapter (*Medical treatment*). On the contrary, the loss of weight improves cholesterol levels, glucose levels and blood pressure[16], thus reducing cardiovascular risk. The reduction in weight also improves walking distance and enhances exercise program results. Patients with multilevel disease (i.e. expanding below knee) are at a higher risk of deteriorating during conservative treatment compared to patients with occlusive disease of the SFA only[17] and therefore should be monitored more closely.

Medical treatment

Optimal medical management is recommended for all patients presenting with

atherosclerotic disease. Most commonly accepted is statin treatment unrelated to individual cholesterol levels. This lipid lowering strategy reduces the incidence of cardiovascular events in patients with PAD. It also showed a beneficial effect on the pain free and total walking distance, though there was no improvement of ABI[18]. Progression of atherosclerosis is thought to be halted by the use of statins. Two studies investigated this presumption. The St Thomas' trial[19] showed significant reduction of disease progression on angiography. In contrast, the Probucol Quantitative Regression Swedish Trial (PQRST) showed no difference with the placebo group[20].

Antiplatelet therapy is given to patients with PAD to reduce the risk of future cardiovascular events, but brings no improvement in clinical symptoms of PAD. Several newer medications are registered for the symptomatic treatment of patients without limb threatening symptoms, including buflomedil, naftidrofuryl and cilostazol. These agents offer a relatively small benefit in the maximum and pain free walking distance. There are no double blind, randomized controlled trials comparing these medications to a placebo group, thus there is not enough burden of proof to recommend it as standard treatment for PAD. Dietary supplements such as garlic, ginko bilboa, and vitamin E do not improve the clinical symptoms of PAD when compared to placebo.

Surgical treatment

Bypass surgery

For long lesions of the SFA (TASC II D) bypass surgery is recommended as the first choice of treatment in patients with Rutherford 3-6[7]. The first successful femoropopliteal bypass was performed in 1948 by Jean Kunlin using an autologous vein graft. To date, this procedure is considered the gold standard for bypass surgery. Several prosthetic materials (polytetrafluorethylene (PTFE), Dacron) have been developed since then. More recently synthetic grafts have been expanded by heparin bonding. Below knee (BK) bypasses are known to have lower patency rates (49-79%) than above knee (AK) bypasses (60-90%). In both AK and BK bypasses autologous vein conduit has a significantly higher primary patency at five years compared to PTFE[21]. Between Dacron and PTFE no significant differences in primary or secondary patency rates exist. One study showed a trend towards better patency rates for PTFE in the BK bypass after a follow-up 24 months[22,23]. Above the knee there is no significant difference between PTFE or PTFE with vein cuff,

but in BK bypasses there is. Below the knee, the human umbilical vein (HUV) conduit also improved primary patency compared to PTFE. Older literature[24], however, described a 30% graft dilatation and aneurysm formation for HUV grafts. More recently these results could not be reproduced[25], but the graft is currently not commercially available anymore, because of transferable viral issues.

Devine et al[26] prospectively randomized 209 patients (30 with BK disease) between heparin bonded Dacron (HBD) grafts versus PTFE grafts for AK and BK bypass. HBD grafts improved the mid-term primary patency compared to PTFE in AK bypass (47% vs 35% at 3 years), while no difference in patency rates were present in BK bypass. Limb salvage rates were 86% and 74%, respectively (P<0.025). Recently, Daenens et al[27] retrospectively compared heparin-bonded PTFE grafts (Hb-PTFE) with autologous vein grafts in AK, BK and femorocrural (FC) bypasses. Two-year primary patency rates for the Hb-PTFE graft were 80%, 72% and 64% respectively, not significantly different from the autologous vein conduits. The Scandinavian Propaten Trial[28] compared Hb-PTFE with standard PTFE grafts in femoropopiteal lesions. They also included patients scheduled for femoro-femoral cross over bypass. Primary patency rates for Hb-PTFE grafts were 86.6% compared to 79.9% in normal PTFE grafts (P=0.043). The risk reduction was most evident in femoropopliteal bypasses.

Concerning postoperative medical treatment there is much heterogeneity in clinical practice. Different postoperative medical treatment is required for synthetic versus venous bypasses. Use of antiplatelet therapy improves synthetic graft 1-year patency. There was no difference in patients who received aspirin alone compared to aspirin with dipyridamol. Antithrombotic therapy (coumarines) improves graft patency for venous bypasses, despite higher risks of hemorrhagic complications[29]. The CASPAR trial showed that combining aspirin with clopidogrel did not improve limb or systemic outcomes in an overall patient population requiring a BK bypass (hazard ratio (HR) 0.98). A subgroup analysis suggested that in synthetic grafts clopidogrel plus aspirin shows a benefit (HR 0.65, P=0.025)[30].

Remote endarterectomy

Since 1994 the remote superficial femoral artery endarterectomy (RSFAE) provides a minimal invasive surgical alternative to the surgical bypass. Through a groin incision a ring stripper is used to dissect the intima of the diseased segment, followed by distal

transection with a remote cutter. The transection zone is stented with a covered nitinol stent. Alternatively, the distal transection is performed surgically followed by Kunlin stitches. Gisbertz et al[31] published the mid-term results of the REVAS trial (Figure 1). One-hundred and sixteen patients were randomized between RSFAE and AK bypass. The primary patency rates of the RSFAE at three years were inferior to the venous bypass (47% vs 65%), but comparable to the synthetic graft (56%). Primary assisted patency rates equal those of the venous bypass. Early restenosis rate (80% at 1-year) of the RSFAE seems to be the confining factor due to aggressive neointimal hyperplasia. In the future the use of drug eluting stents (DES) or balloon cryoplasty might improve patency rates of this technique. Three-year limb salvage rates were comparable between RSFAE and bypass surgery (95%). Theoretically, RSFAE has fewer (early) postoperative complications compared to the surgical bypass due to its minimal invasive character. However, this could not be demonstrated in literature. Nevertheless, hospital stay was significantly shorter in RSFAE compared to surgical bypass. Obviously, RSFAE is an alternative for bypass surgery when there is no autologous vein available. The main advantage is the avoidance of prosthetic materials.

Figure 1. Patient with invalidating claudication not responding to exercise therapy, with total SFA occlusion from the origin to P1 segment. No suitable vein was available, after which the decision was made to perform remote superficial femoral artery endarterectomy (A) through a groin incision. The Moll ring cutter was used (B) and at the transection site an Aspire stent was placed. (C). The endarterectomized specimen. ABI improved from 0.54 before to 0.91 after the operation (Figures kindly provided by Dr. Jean-Paul de Vries, Nieuwegein).

Endovascular treatment

Percutaneous transluminal angioplasty

In past decades endovascular techniques have advanced. For short lesions of the SFA (TASC A) and lesions of the iliac artery PTA is considered the primary treatment[7]. Although the incidence of restenosis following PTA of an iliac artery is only 5-9% at 1-year follow-up, results are more disappointing in the SFA. Results of angioplasty seem to depend on the length of the lesion. For longer lesions (mean 8 cm) primary patency rates following PTA of the SFA are reported to be as low as 33%-55% at 1-year follow-up[32]. In a retrospective review of 159 SFA lesions treated with PTA, Scott et al[33] showed primary patency rates of 55%, 43% and 35% at 12, 24 and 36-months, respectively. A review by Wilson et al[34] comparing PTA of the SFA with optimal medical treatment showed superior short term results for PTA (< 6 months), but at 2 years follow-up no significant differences between the two groups were found. This was true especially for longer lesions (TASC II C/D). Table I summarizes PTA results for long lesions of the SFA. In longer lesions the major limitation of PTA is the occurrence of restenosis due to neointimal hyperplasia. To prevent this hyperplasia drug eluting balloons (DEB) have been developed. These angioplasty balloons are mostly coated with paclitaxel. Their use in coronary artery disease has been shown in several randomized trials[39]. An extrapolation to SFA disease in the Thunder and FemPac trials with the use of DEB showed significant reduction of lumen loss after 6 months. Target lesion revascularisation was also significantly reduced in the group treated with DEB[40,41].

Study	Zdanowski[35] 1999	Minar[32] 2000	Pokrajac[36] 2003	van der Zaag[37] 2004	Schillinger[38] 2006	Total/ Average
# Patients	17	56	46	31	53	203
Lesion length (cm)	7.1	8	10.3	9	9.2	8.9
1yr primary patency	0%	35%	47%	40%	37%	37%

Table I. Patency rates of PTA of long SFA lesions.

Percutaneous transluminal angioplasty with bare stent

As a possible solution to reduce the occurrence of restenosis after PTA, bare stents were implemented. Elastic recoil of the vessel wall could be prevented by the implantation of a metal stent. Initial results with these stents (Wall stents, Palmaz stents) failed to reduce restenosis rates and thus showed no improved patency rates (38% at 1-year, and 8% at three years). Secondary patency rates were improved to 89% and 55% with supplemental PTA[42]. Still severe in stent restenosis occurred, diminishing patency rates. Besides the not significantly improved patency rates bare stent implantation introduced a new problem, i.e. stent fracture. Stent fractures are thought to be the result of the radial forces to which they are exposed within the SFA.

Nitinol stents were introduced as a more flexible alternative, possibly reducing restenosis and stent fracture rates. Stent fractures were reduced to 7.7% in long stented lesions (mean 20.7cm)[43]. Nguyen et al[44] published the results of 824 primary endovascular procedures comparing PTA alone versus PTA plus stenting. There was no difference in overall 5-year primary patency (36% vs 41%, respectively). However, for TASC II C/D lesions stenting yielded significantly better primary patency rates (34% vs 12%, $P<0.05$). In literature one-year primary patency rates vary between 80% for short lesions and 63% for longer lesions. The FAST trial[45] randomized 244 patients between PTA alone and PTA with nitinol stent placement (mean lesion length 45mm). Their primary end point (i.e. binary restenosis) did not reach a statistical difference at 1 year follow-up. The target lesion revascularisation rate (TLR) was higher in the PTA group (18.3% vs 14.9%). The multicenter RESILIENT trial[46] randomized 204 patients in a similar manner. At 1-year follow-up primary patency rates for the stent group were significantly better compared to PTA alone (81.3% vs 36.7%, $P<0.0001$). Freedom from TLR also significantly improved with the use of nitinol stent placement (87.3% vs 45.1%, $P<0.0001$). The third randomized trial included 104 patients (VIENNA trial[38]). They reported significantly lower restenosis rates and better clinical outcome in the PTA with stent group compared to PTA alone. These three randomized trials (Table II) have shown that in longer lesions the use of nitinol stents is related to increased patency rates when compared to PTA only.

Figure 2. A. Pre-operative proximal angiography in a 73-year-old man with CLI Rutherford class 3, showing total SFA occlusion. Pre-operative ABI was 0.64. B. Pre-operative distal re entry point on angiography of the same patient. C. Postoperative angiography after covered stentgraft placement in the same patient. Postoperative ABI was 1.0. D. Postoperative angiography showing distal re-entry point in same patient.

	FAST[45]	RESILIENT[46]	VIENNA[38]	Total/Average
# Patients	123	137	46	306
Lesion length (cm)	4.5	6.2	11.2	7.3
% occlusions	37%	17%	41%	32%
1yr primary patency	68%	80%	63%	70%
2yr primary patency			54%	

Table II. Patency rates of PTA and stenting of long SFA lesions.

Percutaneous transluminal angioplasty with endograft

To further reduce the occurrence of in-stent restenosis covered stents were introduced (Figure 2). The mechanical barrier of the PTFE/Dacron cover around the nitinol stent would prevent in-stent stenosis. The first results using Dacron-covered stents were less promising. Almost 50% of the patients developed post-implantation syndrome (fever and persistent pain) and early restenosis rates (<30 days after the intervention) were 17%. The primary 2-year patency rate was below 50%[47]. A Scandinavian multicentre randomized trial[48] planned to include 120 patients (60 in endograft groups and 60 in synthetic bypass group), but was terminated after an interim analysis of 45 patients. The 1-year primary patency was 48% for the endograft group compared to 95% for the PTFE open bypass group (P=0.02). The worse outcome of the endograft group was explained by the authors by a lack in experience of the angioradiologists and also the maturity of the endoluminal technique.

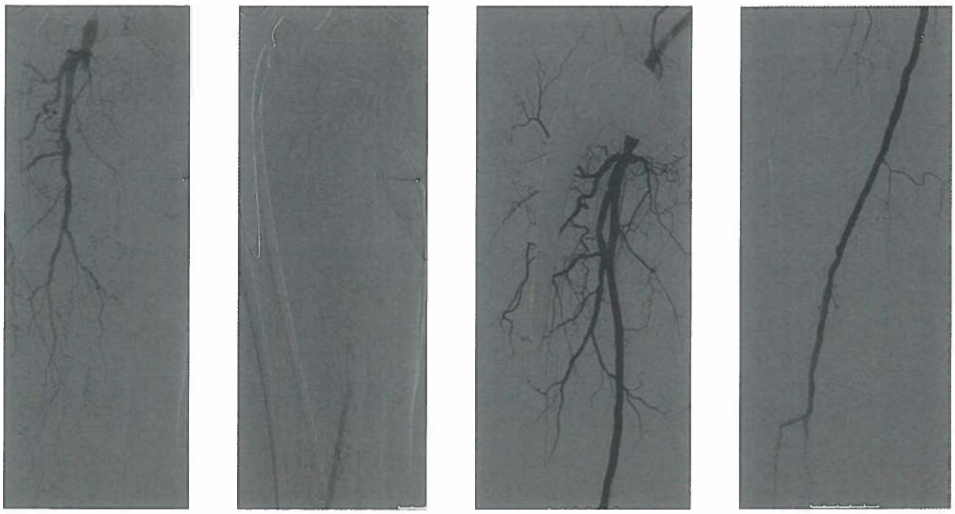

Figure 2. (see left)

In recent years endovascular modalities developed fast, leading to better results. In 2000 Lammer et al[49] published a multicenter study demonstrating 1-year primary and secondary patency rates of percutaneously placed endografts of 79% and 93% in 80 limbs. Saxon et al[50] began to use endografts in a non-randomized manner to treat patients with a longer SFA stenosis (>5 cm) or occlusion (>3 cm) to determine long-term clinical outcome and patency. A total of 87 limbs were treated. Primary patency, primary assisted and secondary target vessel patency rates were 76%, 87% and 93% at 1-year follow-up and 55%, 67% and 79% at 4-year follow-up. There was no significant difference in primary patency rates compared to the length of the lesion. However, results of the endograft were depended on device diameter, with smaller 5-mm devices yielding poorer results (P=0.001). Therefore, it is recommended that endografts are limited to patients with a re-entry vessel with a diameter of at least 4.5 mm[50]. Clinical improvement was achieved in 99% of the patients. This was maintained in 88.5% of the patients, with an average follow-up of more than 28 months. Several other studies showed similar primary patency rates between 74% and 83% at 12-months follow-up after treatment of long SFA lesions (mean length 22cm, range 4-40cm)[51,52]. These results are comparable with primary patency rates as described for conventional surgical bypass using synthetic conduits.

In 2007 Kedora et al[53] compared the efficacy of covered endografts to that of open surgical PTFE AK bypass. This single center prospective randomized trial included 100 limbs (50 open surgical bypass, 50 endograft) with a mean follow-up of 28 months. It includes long lesions (mean length 25 cm) with an adequate mean diameter of 5.7 mm. Postoperative complications were equal in both groups. Mean hospital stay was significantly shorter for the stent graft group (0.9 days vs 3.1 days, P<0.001). The number of interventions were comparable in both groups after 12 months (14 in the endograft group vs 12 in the bypass group). One-year primary patency for the endograft group and open surgical bypass group was 73.5% and 74.2%, respectively. Secondary patency rates were 83.7% for the endograft group and 83.9% for the surgical bypass group. Both showed no significant difference. At 48 months follow-up, primary patency rates for the endograft group and the open surgical bypass group were 59% and 58%, respectively. Secondary patency rates were 74% and 71%, respectively[54]. These results underline the clinical utility of endograft placement as a treatment modality in SFA disease. The minimal invasive aspect of endoluminal stent graft also reduced the incidence of limb swelling and allows for rapid mobilization[51].

To further improve outcome of endograft placement it is essential to determine the underlying causes of loss of patency. The most common cause is edge stenosis[55]. Furthermore, when endoluminally treating long lesions of the SFA, care should be taken to have at least 1 cm of healthy vessel both proximally as distally of the lesion to ensure adequate re-entry possibilities. There should also be a patent popliteal artery and an outflow of at least one open crural vessel. No severe calcification should be present[56]. In a subgroup analysis of patients with these optimal conditions Fisher et al described improved primary and secondary patency rates of 80% and 91%, respectively. Patency rates are summarized in Table III.

Study	Year	# Patients	Lesion length (cm)	1yr primary patency
Lammer[57]	2000	80	13.8	93%
Railo[58]	2001	15	8	93%
Turicchia[59]	2003	16	10	80%
Jahnke[52]	2003	52	8.5	78%
Bleyn[60]	2004	67	14.3	82%
Hartung[61]	2005	34	10.8	85%
Panetta[62]	2005	41	30.4	86%
Zander[63]	2005	31	16.6	86%
Fischer[56]	2006	48	10.7	80%
Kazemi[64]	2006	65	12	90%
Chopra[65]	2006	70	20	93%
Kedora[53]	2007	50	25.6	73%
Saxon[50]	2007	74	14.2	83%
Farraj[66]	2009	32	15.4	80%
Fritschy[55]	2010	96	10.4	76%
Total		**771**	14.3	**84.4%**

Table III. Patency rates of PTA and covered stentgrafts

A possible downside of using covered stents might be the coverage of collateral arteries. Many believe that this will reduce limb salvage or change the level of amputation after

failure of the graft. Literature shows no validation for this concern. After restenosis or occlusion of the endoluminal stent graft the majority of patients returns to baseline chronic limb ischemia. Failure of endovascular therapy does not seem to change the level of anastomosis of surgical bypass or amputation level. It also does not compromise options for surgical bypass[53,54,67]. In patients with a technically difficult distal re-entry the recently described body floss technique can provide a quick way to minimize the stent length, thus sparing collaterals and future surgical options[68]. Large collaterals may be saved by using a so-called hybrid technique including a covered and a distal bare stent.

Drug-eluting and drug-bonded stents (DES, DBS)

To reduce edge stenosis and increase patency drug-eluting and/or drug-bonded stents have been developed. The results from animal models demonstrated marked effects on neointimal hyperplasia and cell proliferation[69]. With heparin-bonded stents an adjunct theoretical advantage is the thromboresistance of the graft lumen, thereby preventing one of the principal causes of early failure, i.e. deposition of thrombus on the luminal surface. Up to date no studies investigating heparin-bonded endografts have been published. Lensvelt et al recently described 56 lesions treated with heparin-bonded endografts for long occlusions of the SFA. At 1 year, primary patency was 75%, primary assisted patency 82% and the secondary patency was 89%[70].

The SIROCCO I and II trials[71] compared Sirolimus-coated Cordis Self-Expanding stents with bare SMART stents in the treatment of TASC-C lesions of the SFA in a randomized fashion. Average lesion length was 8.3 cm. Restenosis rates were 22.9% and 21.1% respectively. No significant differences could be found between DES and bare SMART stents. For paclitaxel-eluting stent grafts Dake et al[72] described the one-year results of 900 lesions with long lesions of the SFA (mean length 99.5 mm). The primary patency rate was 86%. These results suggest promising developments for endoluminal treatment modalities in the future.

Conclusions

With regard to conservative measures reducing cardiovascular risk factors it is anticipated to start with statin treatment despite cholesterol levels, to encourage weight loss and smoking cessation in all patients with PAD. Antiplatelet therapy should also be started at the onset of symptoms. Specifically patients who present with IC should start with exercise therapy, preferably supervised walking training. In patients with Rutherford category 3-6 surgical therapy can be considered. When opting for surgical therapy autologous venous bypass is still the first choice. In patients were no vein is available, RSFAE could be considered before synthetic bypass. Minimal invasive endoluminal treatment is also a good treatment option, especially with frail patients. When endoluminally treating longer lesions of the SFA stenting is recommended, preferably with a covered nitinol stent. In the future drug-bonded stent grafts might improve endoluminal patency rates up to the level of venous bypass. Comparative studies, assessing both patency and quality of life, such as the SUrgical versus PERcutaneous Bypass (SuperB, NCT01220245) trial are therefore essential in defining the role of heparin-covered stent-grafts in the treatment algorithm of chronic occlusive SFA disease[73].

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Chapter 3

Results of heparin-bonded ePTFE-covered stents for chronic occlusive superficial femoral artery disease

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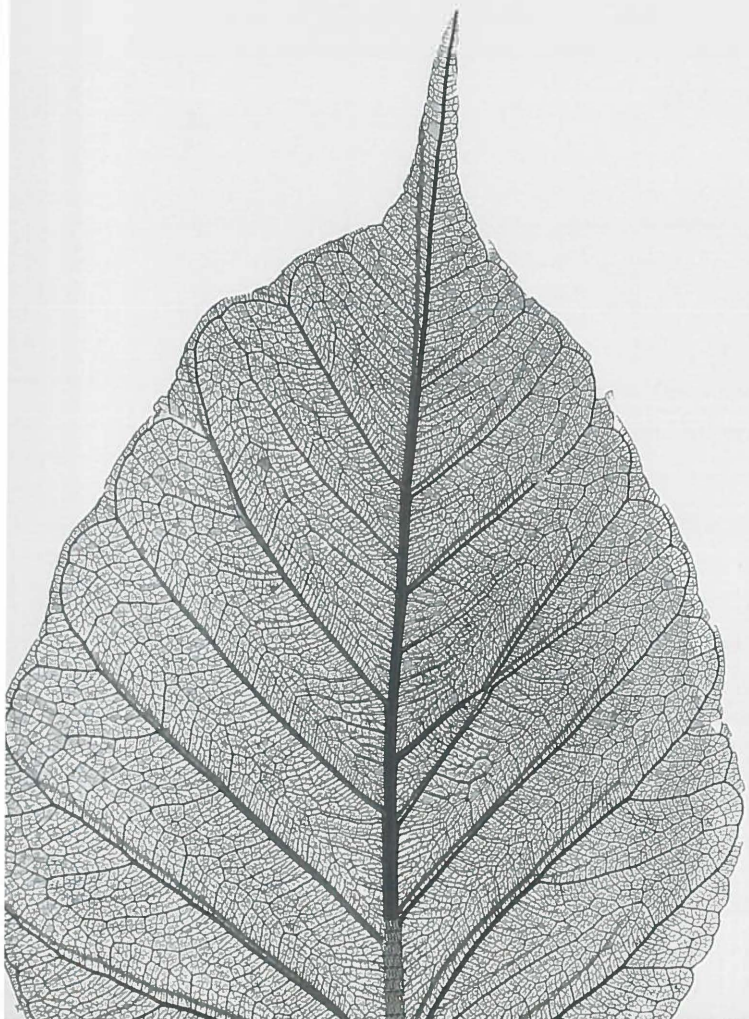

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Abstract

Objective

To assess the 1-year patency rates of heparin-bonded covered stents in the treatment of chronic occlusive disease of the superficial femoral artery (SFA).

Methods

All patients treated with a heparin-bonded endograft between April 2009 and October 2010 for chronic occlusive disease of the SFA were prospectively gathered in a database and retrospectively analyzed. Primary, primary-assisted and secondary patency rates, assessed by ultrasound scanning, were analyzed at 1-year, as were the complication rates and mortality.

Results

A total of 56 limbs were treated with a heparin-bonded covered stent in 53 patients for chronic ischemia Rutherford category 3 (n=36), 4 (n=5), 5 (n=11) and 6 (n=1). Lesions were classified as TASC II B (n=9), C (n=14) and D (n=33) and the mean treated lesion length was 18.5 ± 7.7 cm. Postoperative complications occurred in 7.5%, including hematoma (n=1), edema (n=1), pneumonia (n=1) and urinary retention (n=1), and the 30-day mortality rate was 0%. The mean follow-up was 413 ± 208 days. At 1 year, the primary patency was 76%, the primary-assisted patency 82%, and the secondary patency 89%. The limb salvage rate was 100%.

Conclusions

Heparin-bonded covered stents seem to provide a valid alternative to surgical treatment of long occlusive lesions in the SFA. Randomized trials and long-term data are required before considering the technique as a new standard of care.

Introduction

Peripheral arterial disease (PAD) is a widespread problem with a prevalence of 3% to 10%, increasing to 15% to 20% over the age of 70 years[1-3]. The prevalence of intermittent claudication is estimated 3% in patients aged 40 to 6% in patients aged 60 years[4,5]. One percent of patients with PAD will eventually develop critical limb ischemia annually. The Trans Atlantic InterSociety Consensus (TASC) has given recommendations for treatment strategies, based on morphological stratification of the lesions[5]. Surgery is considered the gold standard for lesions with a length of >15 cm. Endovascular alternatives and results, however, are evolving continuously.

The introduction of nitinol stents has improved results of endovascular treatment of chronic occlusive lesions of the SFA. One-year primary patency rates have been reported between 63% and 80% in lesions with a length of 5cm to 11cm[6-8]. The major limitation of endovascular treatment is the occurrence of (in stent) restenosis due to intimal neo-hyperplasia. To reduce the incidence of in stent restenosis covered stents have been introduced. We have recently shown that these may reduce restenosis to edge stenosis only[9]. Case series have shown 1-year primary patency rates between 44 and 93% for lesions from 8 cm up to 26cm[10-12]. McQuade et al. have recently published the 4-year results of a randomized trial comparing an above-knee prosthetic femoropopliteal bypass with covered stents[13]. There were no differences in primary or secondary patency rates between both treatment modalities and limb salvage rates were also comparable, indicating that covered stents may be a viable alternative for bypass surgery. The venous femoropopliteal bypass, however, is associated with higher patency rates, when compared to prosthetic bypasses[14].

The introduction of the heparin-bonded technology has significantly improved patency rates of peripheral surgical bypasses[15,16]. Since endograft failure is often due to acute thrombosis rather than in stent restenosis, the heparin-bonding technology has also been integrated with endografts. It is believed that the irreversible bonded heparin-molecules in the inner surface of the graft may prevent thrombosis, thus further increasing their performance. To date, no clinical studies have been published using heparin-bonded endografts. The aim of the present study was to assess the 1-year results of heparin-bonded covered stents in the treatment of chronic occlusive disease of the SFA.

Patients and Methods

Patients

All patients treated with a heparin-bonded polytetrafluorethylene (ePTFE) covered stent between April 2009 and October 2010 in the Alysis Hospital, location Rijnstate in Arnhem and the Isala Clinics in Zwolle, The Netherlands were prospectively gathered in a database. Two dedicated vascular surgeons (MR and WF) and one interventional radiologist (JvO) performed all procedures.

In all patients secondary risk prevention was performed according to the national guidelines and all patients with intermittent claudication were initially treated with walking exercise. Only those with unsuccessful exercise training were indicated for intervention. The indication for endovascular treatment was based on anatomical suitability and the preference of both the patient and surgeon. Generally, covered stents were used in lesions with a length of more than 15 cm, while bare metal stents or plain balloon angioplasty were used in shorter lesions. Anatomical suitability consisted of an adequate inflow without a flow-limiting stenosis in the aorto-iliac arteries, a patent popliteal artery above the P3 level with a luminal diameter of at least 4.2 mm and at least one patent crural vessel.

Demographics, clinical status and medical history were noted and retrospectively reviewed. Procedural aspects and follow-up data were retrieved. Lesions were reviewed and scored according to the TASC II criteria[5]. Additionally the lesion length, luminal vessel diameters and the number of patent run-off vessels were scored.

Patients with a lesion length of < 5 cm were excluded from the analysis as were patients who had undergone a previous stent placement in the ipsilateral SFA or femoropopliteal bypass surgery.

Follow-up consisted of clinical assessment, including physical examination, ankle-brachial index (ABI) measurements, and duplex ultrasound scans at 1, 3, 6 and 12 months. The ABI was measured in a supine position using a Nicolet™ VasoGuard (CareFusion Corporation, San Diego, CA) or a Basic 3 (Atys Medical, Soucieu en Jarrest, France). Complications and additional treatments were registered in the hospital files.

Definitions

Risk factors were scored according to the Society for Vascular Surgery medical comorbidity

grading system. Restenosis was defined as a peak systolic velocity (PSV) ratio >2.5, as measured on ultrasound scanning. An occlusion was defined as absence of flow in the treated segment of the superficial femoral artery. Primary patency was defined as the absence of restenosis or occlusion in the target vessel. Primary-assisted patency was defined as patency achieved by secondary endovascular interventions to treat re-stenosis of the target vessel. Secondary patency was defined as patency achieved by all procedures aimed at recanalizing an occluded endograft, thereby preserving the endograft. Limb salvage was defined as the absence of an above ankle amputation.

Treatment protocol

Procedures were performed using antibiotic prophylaxis. The common femoral artery was approached either percutaneously or surgically, as preferred by the treating surgeon. When there was a concomitant lesion in the common or profunda femoral artery an endarterectomy was performed. Heparin (5000 IU) was administered. The diseased segment of the SFA was passed using a Terumo® wire (Terumo Medical Corporation, Elkton, MD) and a catheter, either endoluminal or subintimal and a re-entry was created distally. The segment was pre-dilated with a regular angioplasty balloon and the endografts were positioned from distal to proximal with minimal oversizing. The entire diseased segment was covered with endografts and endografts were postdilated with an angioplasty balloon with the same size as the endograft. Control angiography of the bypass and outflow vessels was performed routinely. In case of a percutaneous approach, the access was closed using a closure device (Angio-Seal™, St Jude Medical, Minnesota, USA, or Proglide® , Abbott Vascular, Bruxelles, Belgium) or by manual compression.

The used endograft was the heparin-bonded Viabahn Endoprosthesis (W.L. Gore & associates, Flagstaff, AZ, USA), which is a self-expanding helical nitinol stent covered with a heparin-bonded thin ePTFE tube.

Postprocedural patients received statin treatment and dual anti-platelet inhibitors, unless oral anticoagulation was indicated for other reasons.

Statistical Analysis

Patient characteristics and characteristics of the treated lesions are presented as mean and standard deviation, unless otherwise stated. Patency rates were determined using the Kaplan Meier life-table method using PASW statistics version 18.0 (SPSS Inc., Chicago,

IL). Log-rank testing was used to determine possible differences in patency rates between different subgroup (i.e. different TASC II lesions, level of distal anastomosis, lesion length, diabetes mellitus, smoking, stent diameter, number of patent outflow vessels). A p-value < .05 was considered statistically significant. Data are presented as mean and standard deviation, unless otherwise stated.

Results

Patient population

During the study period a total of 59 SFA's in 56 patients were scheduled for endovascular treatment, of which 56 SFA's were successfully treated (95%). In the remaining 3 patients the procedure was converted to an open femoropopliteal bypass because of the inability to recanalyze the diseased segment. The mean age was 69.6 ± 9.4 years and the male:female ratio was 40:13. Twenty-one patients (37.5%) were treated in the Isala Clinics in Zwolle and the remaining 35 (62.5%) in the Rijnstate hospital, Arnhem.

Patient characteristics and risk factors are shown in Table 1. Four patients (7.1%) had previously undergone an angioplasty of the SFA without stent placement, and 3 others (5.4%) had undergone an angioplasty with (n=2) or without (n=1) stent placement of the iliac artery. One patient already had a patent aorto-iliac bypass, and another patient had previously undergone an endarterectomy of the ipsilateral common femoral artery. Two patients (3.6%) had already undergone a minor amputation of the ipsilateral limb.

The mean pre-procedural ABI was 0.49 ± 0.1 with a range of 0.19-0.74. Nine (16.1%) lesions were classified as TASC II B lesions, 14 (25%) as TASC II C lesions and the remaining 33 (58.9%) were TASC II D lesions. The mean length of the lesions was 18.5 ± 7.7cm. Other anatomical lesion characteristics are shown in Table 2.

Risk factor		N (%)
Diabetes Mellitus	Yes	22 (41,6)
	No	31 (58,4)
Smoking	Never	16 (30,2)
	Former	10 (18,9)
	Current	27 (50,9)

Risk factor		N (%)
Hypertension	Yes	43 (81,1)
	No	10 (18,9)
Hyperlipidemia	Yes	41 (77,3)
	No	12 (22,7)
History of cardiac disease	No	33 (62,3)
	>10 years ago	8 (15,1)
	Stabile AP, recent MI	9 (16,9)
	Non stabile AP	3 (5,7)
Neurological status	Asymptomatic	48 (90,6)
	Asymptomatic CVA/TIA	4 (7,5)
	Symptomatic CVA	1 (1,9)
Renal disease	No disease	42 (79,2)
	Renal disease	8 (15,1)
	Dialysis dependent	3 (5,7)
Pulmonary disease	Yes	13 (24,5)
	No	40 (75,5)
ASA Classification	I	1 (1,9)
	II	22 (41,5)
	III	28 (52,8)
	IV	2 (3,8)
Rutherford Classification	3	36 (67,9)
	4	5 (9,4)
	5	11 (20,8)
	6	1 (1,9)

Table 1. Patient characteristics and risk factors. ASA = American Society of Anesthesiologists. AP = angina pectoris, MI = myocardial infarction, CVA = cerebrovascular accident, TIA = transient ischemic attack.

Anatomical character		N (%)
Level of distal end of endograft	P1	36 (64.3)
	P2	17 (30.3)
	P3	3 (5.4)
Number of patent outflow vessels	0	1 (1.8)
	1	5 (8.9)
	2	11 (19.6)
	3	39 (69.7)
Lesion length (mm)		185±77
Luminal diameter superficial femoral artery (mm)		5.4±1.1
Luminal diameter popliteal artery (mm)		4.6±0.75

Table 2. Characteristics of the treated lesions. Data are presented as mean and standard deviation. P1 = popliteal artery cranial of the upper border of the patella. P2 = popliteal artery between the tibia plateau and upper border of the patella. P3 = popliteal artery below the tibia plateau

Procedure

Four patients were treated using local anesthesia only (7.5%), 26 were treated using spinal anesthetics (49.1%) and the remaining 23 had general anesthetics (43.4%). The use of spinal or general anesthetics enabled a conversion to a hybrid approach or a surgical bypass in case of a technical failure within the same session. A percutaneous approach was used in 34 procedures (60.7%). In most of these cases access was acquired ultrasound-guided. Endografts were inserted with an exposed common femoral artery, as preferred by one of the surgeons, using a longitudinal incision in 11 patients (19.6%) and a concomitant endarterectomy of the communal femoral artery was performed in 11 other patients (19.6%). An additional angioplasty of the iliac arteries, with bare metal stent placement in 2 of them, was performed in 5 patients in order to improve inflow and angioplasty of the popliteal artery was performed in 2 patients to improve outflow. Three patients underwent a necrotectomy and a planned minor amputation was performed in 2 patients. In one patient a bilateral procedure was combined with the treatment of an abdominal aortic aneurysm using EVAR. Postoperatively, one patient was treated with continuous thrombolytic therapy, because of thrombosis of the crural arteries that already existed before the intervention. This was also the only patient who stayed in the medium care unit during the 2 days of receiving thrombolytic therapy.

In 16 cases (28.6%) one endograft was used, in 18 procedures (32.1%) two endografts were used and in the remaining 22 cases (39.3%) three endografts were used. In 3 cases (5.4%) the used diameter of the endograft was 5mm, in 45 patients (80.4%) 6mm, in 7 patients (12.5%) 7mm, and in 1 patient (1.7%) 8mm.

One procedure was complicated by a dissection of the popliteal artery that was treated in the same session with an additional endograft. Postoperative complications occurred in 4 out of 53 patients (7.5%). One patient had a hematoma at the puncture site that was treated conservatively. One patient sustained urine retention conservatively treated with a urinary catheter for 24 hours. One patient developed pneumonia and was treated with antibiotics. One patient had an edema, without signs of deep venous thrombosis on duplex ultrasound. The swelling and redness, probably due to reperfusion, disappeared during the first postoperative month. The 30-day mortality rate was 0%.

Patients were admitted to the hospital for a mean of 3.0 ± 2.6 days. Most patients were admitted the day before the intervention. Patients who underwent a percutaneous procedure had a mean length of stay of 2.4 ± 1.2 days and patients with an open approach were admitted for 3.6 ±2.5 days. The mean postoperative ABI was 1.00, with a range of 0.74-1.17.

Postoperatively, 37 (69.8%) patients were treated with the combination of acetylsalicylic acid 80 mg and clopidogrel 75 mg, 8 patients (15.1%) received acetylsalicylic acid 80 mg with dipyridamol 400 mg and 4 (7.5%) patients were treated by acetylsalicylic acid 80 mg only. Four (7.5%) patients were treated by coumarin derivates because of other indications. All patients were treated with statins.

Clinical outcome

All but one patient clinically improved after placement of the endograft(s) (Fig. 1).

The median Rutherford improved from category 3 (range 3-6) pre-operatively to category 0 (range 0-4) postoperatively ($P<0.001$). There was one patient that did not improve clinically having an early endograft failure and she was treated with a surgical femoropopliteal bypass. The subset of patients that were treated for critical limb ischemia (n=18) had all improved. Sixteen patients (88.9%) improved from critical ischemia to claudication (Rutherford 1 to 3) and the others were asymptomatic. At one-year follow-up the freedom from target lesion revascularization was 92.6%.

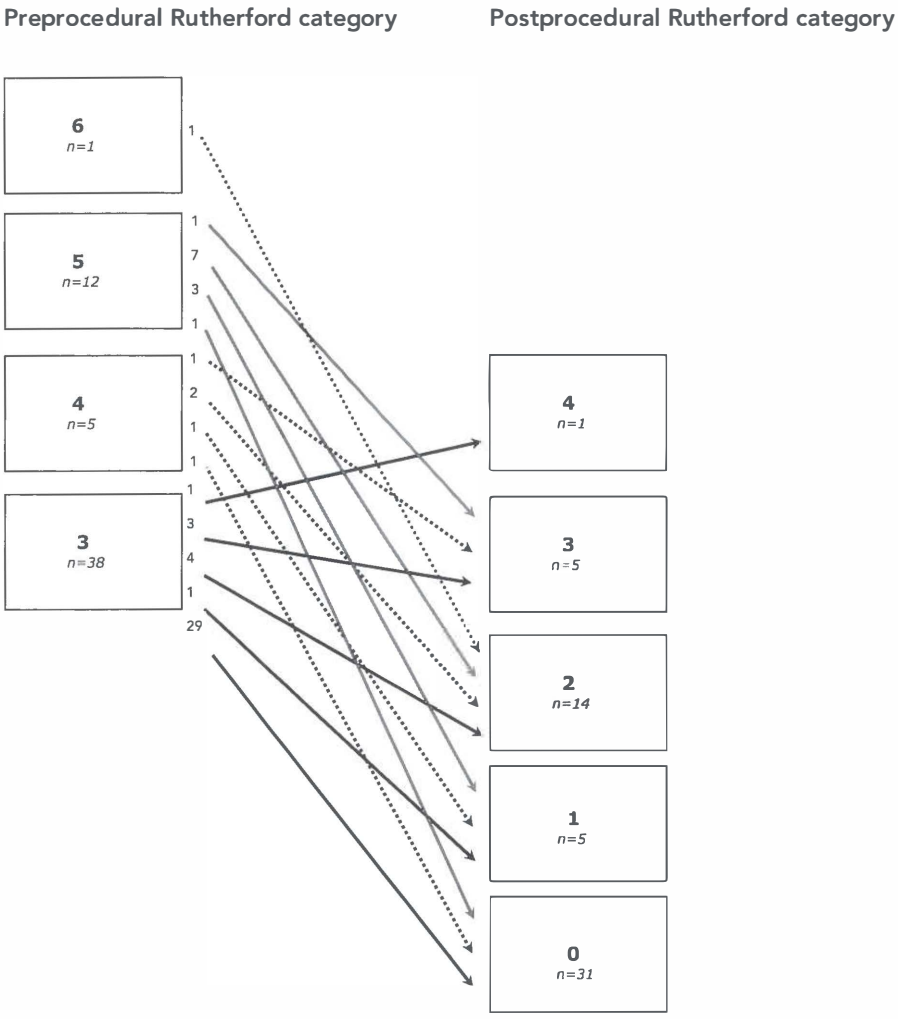


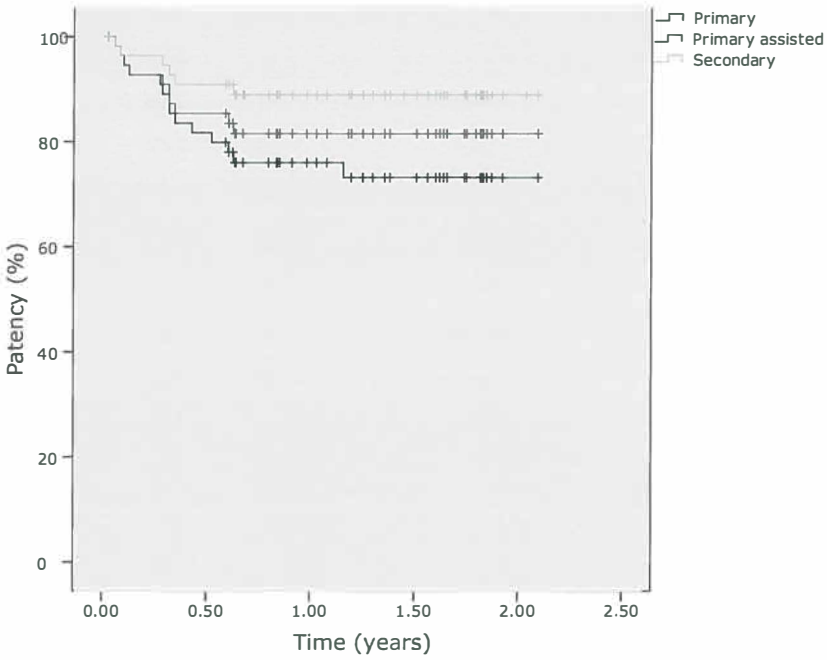
Figure 1. Individual changes in the Rutherford categories before and after the procedure.

Patency

The mean follow-up was 413 ± 208 days. The one-year primary patency was 76.2%, the 1-year primary-assisted patency was 81.7% and the secondary patency rate was 89.0% (Fig. 2). During follow-up, no major amputations were performed.

A univariate analysis of risk factors, commonly associated with failure, showed no significant difference between subgroups, as defined in the statistical analysis (Table 3). The number of endografts used seemed to have an effect on the patency rate, although

not statistically significant (P=.097). The use of 3 endografts decreased the primary patency rate with respectively 28% and 24% when compared with the use of 1 and 2 endografts (Fig. 3). Moreover, patients with a single vessel run off (n=5) tended to have a lower, but not statistically significant, patency rate compared to patients with 2 or 3 vessel run-off.

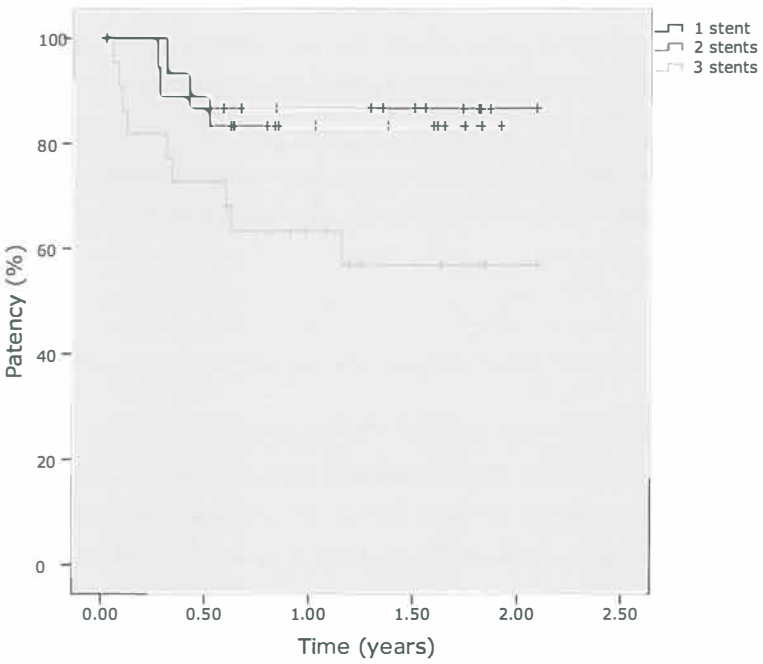


Limbs at risk					
Primary patency	56	45	29	19	2
Primary assisted patency	56	47	31	20	2
Secondary patency	56	50	34	21	3
Patency (%)					
Primary patency	100	81.8	76.2	73.4	73.4
Primary assisted patency	100	85.5	81.7	81.7	81.7
Secondary patency	100	90.9	89.0	89.0	89.0
SE (%)					
Primary patency	0	5.2	5.8	6.2	6.2
Primary assisted patency	0	4.8	5.2	5.2	5.2
Secondary patency	0	3.9	4.2	4.2	4.2

Figure 2. Kaplan-Meier survival curve showing primary patency, primary-assisted patency and secondary patency of the heparin-bonded endografts.

Risk Factor		N	Patency (%)	P
TASC-2 Classification	B	9	77.8	.575
	C	14	85.7	
	D	33	69.7	
Level distal anastomosis	P1	36	72.2	.598
	P2	17	82.4	
	P3	3	66.7	
Lesion length	<15cm	17	76.5	.790
	>15cm	39	74.4	
Diabetes Mellitus	Yes	24	78.1	.528
	No	32	70.8	
Smoking	No	16	81.3	.758
	Former	13	76.9	
	Current	27	70.4	
Endograft diameter	5	3	100	.562
	6	45	71.1	
	7	7	85.7	
	8	1	100	
Number of used endografts	1	16	87.5	.09
	2	18	83.3	
	3	22	59.1	
Number of patent outflow vessels	0	1	100	.513
	1	5	40	
	2	11	72.7	
	3	39	79.5	

Table 3. Primary patency rates of the heparin-bonded endografts in relation to risk factors for failure. TASC = Trans Atlantic InterSociety Consensus. P1 = popliteal artery cranial of the upper border of the patella. P2 = popliteal artery between the tibia plateau and upper border of the patella. P3 = popliteal artery below the tibia plateau



Limbs at risk					
1 stent	16	13	9	7	1
2 stents	18	16	9	7	0
3 stents	22	16	11	5	0
Patency (%)					
1 stent	100	86.7	86.7	86.7	86.7
2 stents	100	88.9	83.3	83.3	83.3
3 stents	100	72.7	63.3	57.0	57.0
SE (%)					
1 stent	0	8.8	8.8	8.8	8.8
2 stents	0	7.4	8.8	8.8	8.8
3 stents	0	9.5	10.3	11.1	11.1

Figure 3. Kaplan-Meier survival curve showing primary patency in relation to the number of endografts used.

Outcome of failures

During follow-up the endograft failed in six patients (10.1%). In all but one patient the Rutherford category at time of failure was similar or lower when compared to the pre-operative Rutherford category. The other patient went from Rutherford category 3 to category 4.

In two patients, with a pre-procedural Rutherford classification of respectively 3 and 4, the occlusion was found during routine duplex surveillance without having clinical symptoms. The other four patients returned with symptoms and were all initially treated by chemical

thrombolysis. In one patient the endograft then remained patent for another nine months, before it finally failed. This patient was treated with a below-knee ePTFE bypass due to the absence of usable vein conduit. In the other three patients thrombolysis failed and they were treated with a venous above-knee femoropopliteal bypass. The distal runoff did not change after failure of the endograft, when compared to the pre-operative state.

Discussion

The present study shows the results of the first prospective cohort of patients treated in our centers with a heparin-bonded covered stent for chronic occlusive disease of the SFA. Based on our data, we conclude that the use of heparin-bonded covered stents for this indication is feasible, safe and related with a good clinical outcome. This indicates that the use of heparin-bonded endografts might be a valid alternative for surgery in this specific group of patients. The technique, however, may also be considered as an extra treatment option before even considering a surgical reconstruction. In our series, failure of the endoluminal bypass did not lead to any major amputations or worsening of the clinical status, which confirms the observation of McQuade et al., that the use of covered stents in SFA occlusive disease is not related to an increased amputation rate, due to covering collaterals, in case of failure[13].

Femoropopliteal bypass surgery is related to morbidity, including early postoperative complications such as wound healing problems in 5% to 44% and edema in up to 40%-100%[17-20]. The minimal invasive character of an endovascular reconstruction may well decrease morbidity in these, often frail, patients. The overall complication rate of in our study was only 7.5%, which then again may seem high for an endovascular procedure, emphasizing the vulnerability of this patient group. There were no wound healing disturbances and only one patient had a self-limiting postoperative edema. Comparative studies with either bare metal stents and surgical bypass, assessing both patency rates and quality of life, such as the SUPERB (SUrgical versus PERcutaneous Bypass) and the VIBRANT (Viabahn Versus Bare Nitinol Stent in the Treatment of Long Lesion [≥ 8 cm] Superficial Femoral Artery Occlusive Disease) trials are essential in defining the role of heparin-covered endografts in the treatment algorithm of chronic occlusive SFA disease[21].

In the last decade, multiple case series and few randomized trials have been published

focusing on non-heparin-bonded endografts for SFA occlusive disease. Treatment strategies greatly varied, making comparisons inappropriate. The previous studies showed 1-year primary patency rate varying between 44% and 93% with large variation in treatment length (between 7 and 26 cm)[10-12]. Moreover, there were large differences in the post-interventional antiplatelet strategy. In most series patients were treated with acetylsalicylic acid while in half of them clopidogrel was added for 6 weeks to over 3 months. A study focusing on endovascular treatment of popliteal artery aneurysms, showed that the use of clopidogrel was the only predictor of outcome[22]. In contrast to previous studies, patients were consequently treated with statins in our series, according to current guidelines on secondary risk prevention. Statins not only lower cholesterol, but may also reduce the incidence of restenosis by their anti-inflammatory, anti-proliferative, and anti-thrombogenic effects[23].

In the study of McQuade et al., 5mm endografts seemed to perform worse compared 6 and 7 mm endografts at 2-year follow-up[24]. In the present study, we could not confirm this observation using heparin-bonded endografts, although our 5mm group was very small. Further risk analysis did not reveal any significant predicting factor for failure. The use of 3 stents was associated with a, non-significant, 25% decrease in 1-year patency when compared to the use of 1 or 2 endografts. The numbers, however, were low and the lack of statistical significance may well represent a type II error. Multiple zones of overlap may decrease flexibility of the device, thereby possibly reducing performance and have also been associated with an increased incidence of stent fractures following endovascular treatment of popliteal artery aneurysms[25]. Fortunately, with the introduction of a 25 cm endograft in 2010, the use of more than 2 stents is usually no longer necessary. Moreover, patients with a single vessel run-off appeared to be prone for failure in our series. However, the low number of patients with a single vessel run-off in this study renders any conclusion unreliable.

With the introduction of the heparin-bonded technology in the endograft the design of the stent has also been changed in order to reduce edge stenosis. The proximal edge of the endograft has no longer a straight, but a contoured edge, that reduces infolding in case of oversizing, maintaining laminar blood flow and thus preventing intimal hyperplasia. The results of the present study may therefore not be attributed to the heparin-bonding technology, only.

Whether the use of covered stents for long chronic occlusions of the SFA is cost-effective

may not be concluded from the present data. The use of covered stents is likely to increase procedural costs. Additionally, endovascular techniques are often related to a higher incidence of re-interventions in order to maintain patency. In our series only 4 patients required an additional angioplasty procedure to prevent failure. On the other hand, the mean hospital stay and complication rate is usually lower, due to its minimal invasive character. Further studies, focusing on cost-effectiveness are indicated. Prospective randomized trials are needed to compare the current gold standards, bare metal stents and venous bypass versus heparin-bonded ePTFE-covered stent grafts, which should also include cost-effective analyses. Moreover, comparative studies with the newly developed drug-eluting stents are essential before considering the use of endografts as a routine treatment.

In conclusion, the heparin-bonded endoluminal bypass is associated with acceptable patency rates and is related to a low morbidity and mortality rate. Furthermore, it does not exclude the later placement of a venous bypass. Randomized trials are indicated, before considering the technique a new standard of care and to elucidate the place of the technique in the treatment algorithm of chronic SFA occlusive disease.

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Chapter 4

The outcome of failed endografts inserted for superficial femoral artery occlusive disease

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Abstract

Objective

Endografts represent a relatively new treatment modality for occlusive disease of the superficial femoral artery (SFA), with promising results. Endografts, however, may occlude collateral arteries, which may affect outcome in case of failure. The purpose of this study was to analyze the clinical outcome of failed endografts in patients with SFA occlusive disease.

Methods

All patients treated with a polytetrafluorethylene (ePTFE) covered stent between November 2001 and December 2011 were prospectively included in a database. Patients with a failure of the endograft were retrospectively analyzed. Clinical and hemodynamic parameters were assessed before the initial procedure and at the time of failure. Outcome of secondary procedures were analyzed.

Results

A total of 341 patients were treated in the study period of which 49 (14%) failed during follow-up. Forty-three percent of patients (n=21) presented with the same Rutherford category as before the initial procedure, 37% (n=18) with an improved category and 20% (n=10) with a deteriorated category. The ankle brachial index was significantly lower at time of failure (0.66 ± 0.19 vs. 0.45±0.19, $p<0.002$). Seventy-six percent of patient with a failure needed secondary surgery. The 1-year primary, primary-assisted and secondary patency rates of secondary bypasses were 55.1%, 62.3% and 77.7%, respectively. The amputation rate was 4.1% (n=2).

Conclusion

Failure of endografts is not associated with a deterioration in clinical state and is related to a low amputation rate. The hypothesis that covered stents do not affect options for secondary reconstructions could not be confirmed as 25% of patients with a failure ended with a BK bypass. Secondary surgical bypasses are correlated with a poor patency.

Introduction

Nitinol stents have improved the outcome of endovascular treatment of occlusive disease of the superficial femoral artery (SFA). Randomized trials have shown their superiority in lesions from 6.5 to 9.5 cm length[1,2] while in shorter lesions no differences compared to angioplasty only[3]. In more extensive lesions bare metal stents are likely to perform worse due to the occurrence of in stent restenosis. Therefore surgical reconstruction is still the gold standard for lesions over 15 cm in length[4]. Bypass surgery, however, is associated with complications and a prolonged hospital admittance.

The use of covered stents may increase the results of endovascular treatment of more extensive disease in the SFA. Various case series have been published with mixed results, most likely due to large variances in both lesion and patient characteristics. In a multicentre randomized trial McQuade et al. have shown that using endografts similar patency rates were achieved compared to above knee (AK) femoropopliteal bypasses after 4-years follow-up, without differences in complication rates[5]. With the development of the heparin-bonding technology the results of endografts may further increase. In a recent study a 1-year primary patency of 75%, a primary-assisted patency of 81.7%, and a secondary patency 89% was described in a series of mostly Trans Atlantic Intersociety Consensus (TASC II) D lesions[6].

A possible shortcoming of covered stents might be the coverage of collateral arteries. It is believed that this will reduce limb salvage rate or may change the level of amputation after failure of the graft. However, in the above mentioned randomized trial failure of endografts did not increase the amputation rate. The aim of the present study is twofold. First, we aim to study the clinical state of patients that presented with a failure of covered stents used for SFA occlusive disease, that had possibly covered collateral arteries. Second we intend to assess the outcome of eventual secondary reconstructions in case of failure.

Materials and Methods

All patients treated with a polytetrafluorethylene (ePTFE) covered endograft between November 2001 and December 2011 in the Rijnstate Hospital Arnhem, the Isala Clinics Zwolle, and the Antonius Hospital Sneek, the Netherlands were prospectively gathered in a database. The indication for endovascular treatment was based on anatomical suitability and the preference of both the patient and surgeon. In all patients there was an indication for surgery and treatment with an endograft was offered as a minimal invasive alternative. Routine follow-up consisted of clinical assessment, ankle-brachial index (ABI) measurements and ultrasound studies at 1, 3, 6 and 12 months and yearly thereafter. Complications and additional treatments were registered in the hospital files.

All patients who presented with a failed endograft, either clinically or during routine surveillance, were included in the study and retrospectively analyzed. Demographics, clinical status and medical history were noted. Procedural aspects of the initial procedure and follow-up data were retrieved, as was the follow-up of a secondary procedure if applicable. Cardiovascular risk factors were scored according to the Society for Vascular Surgery medical comorbidity grading system. Clinical symptoms at the time of the initial procedure and symptoms at the time of failure were categorized according to the Rutherford classification. ABI measurements at the time of failure were compared with ABI measurements before insertion of the endografts. Lesions were reviewed at the time of the initial procedure and at the time of failure, and scored according to the TASC II criteria by two authors (ML, BG)[4]. The number and patency of the run-off vessels were scored at both time points. Patency of run-off vessels was classified as the either open, open with stenosis (peak systolic velocity ratio >2.5) or occlusion. The outcome of all secondary procedures was assessed as was the limb salvage rate.

Treatment protocol

The treatment protocol has been previously described[6]. Briefly, the common femoral artery was approached either percutaneously or surgically. When there was a concomitant lesion in the common or profunda femoral artery, an endarterectomy was performed. Heparin and antibiotic profylaxis were administered. The diseased segment was passed, either endoluminal or subintimal, using a 0.035" Terumo® glide-wire (Radiofocus® Guidewire M, Terumo Medical Corporation, Elkton, MD, USA) and a catheter, and a

subsequent a re-entry was created distally. The segment was pre-dilated and endografts (Viabahn Endoprosthesis, W.L. Gore & associates, Flagstaff, AZ, USA) were positioned from distal to proximal with minimal or no oversizing. Sizing was performed using a computed tomography or magnetic resonance scan. The entire diseased segment was covered with endografts, which were postdilated with an angioplasty balloon of the same size as the endograft. Control angiography of the endograft and outflow vessels was performed routinely. Postprocedural, patients received statin treatment and dual anti-platelet inhibitors, unless oral anticoagulation was indicated for other reasons.

Definitions

Failure of the endograft was defined as occlusion of the endograft, with or without clinical symptoms, not responding to fibrinolytic or surgical therapy or not eligible for therapy. An occlusion was defined as the absence of flow in the treated segment of the superficial femoral artery. Primary patency was defined as the absence of restenosis or occlusion in the target vessel. Restenosis was defined as a peak systolic velocity (PSV) ratio >2.5, as measured on ultrasound scanning. Primary-assisted patency was defined as patency achieved by secondary endovascular interventions to treat restenosis of the target vessel. Secondary patency was defined as patency after thrombolytic or surgical treatment performed for bypass occlusion. Limb salvage was defined as the absence of an above ankle amputation.

Endpoints

The primary endpoints of the study were the comparison of the initial- and post-failure Rutherford category and the clinical outcome of failures, including amputation rate, and patency rates of eventual secondary interventions. Secondary endpoints were the differences between initial and post-failure ABI, differences between the quality of outflow vessels at the initial procedure and post-failure.

Statistical Analysis

Continuous variables are presented as mean or as median with range, non-parametric values as median and range and categorical variables as counts and percentages. Univariate analyses were performed to identify a possible influence of various confounding factors acting on the Rutherford classification at the time of failure. Kaplan-Meier survival

analysis was performed to asses primary patency after secondary surgical intervention. P-value <0.05 was considered statistically significant. The data were analyzed using IBM SPSS Inc. statistics (version 19, 2010).

Results

During the study period a total of 341 patients were treated with an endograft for occlusive SFA disease. The median follow-up was 24 months (range 0-72 months). During follow-up 49 patients presented with an occluded endograft. The majority of these were male (67.3%) and the mean age was 66 ± 9 years. The incidence of cardiovascular risk factors is shown in Table 1.

Cardiovascular Risk Factors	No. of patients (%)
Hyperlipidemia	
Normal cholesterol	11 (22.4)
Mildly elevated, dietary	1 (2)
Type II, III, IV, dietary	0 (0)
Treated with drugs	36 (73.5)
Diabetes Mellitus	
No	36 (73.5)
Adult, dietary	5 (10.2)
Adult, insulin dependent	8 (16.3)
Juvenile diabetes	0 (0)
Hypertension	
No	11 (22.4)
Treated with one drug	11 (22.4)
Treated with two drugs	10 (20.4)
Treated with three drugs	17 (34.7)
Renal Failure	
No	47 (95.9)
Creatinin 1.5-3.0; GFR 30-50	1 (2)
Creatinin 3.0-6.0; GFR 15-30	1 (2)
Creatinin >6.0; GFR <15, transplant	0 (0)
Pulmonary disease	
Asymptomatic	42 (85.7)
Mild dyspnoe	5 (10.2)
Moderate dyspnoe	2 (4.1)
O2-needed, pulmonary hypertension	0 (0)

Cardiovascular Risk Factors	No. of patients (%)
Cardiac status	
Asymptomatic	31 (63.3)
Non recent MI (>6m), or asymptomatic MI on ECG	11 (22.4)
Stable AP, arrhytmias, treatable heart failure	7 (14.3)
Instable AP, recent MI (<6m)	0 (0)
Carotid status	
No disease	43 (87.8)
Asymptomatic, signs of disease	2 (4.1)
TIA/CVA w/o rest symptoms	3 (6.1)
CVA w rest symptoms	1 (2)
Pre-operative medication	
Acenocoumarol	4 (8.2)
Acetylsalicylic acid	38 (77.6)
Fenprocoumon	0 (0)
Clopidogrel	1 (2)
Dipyridamol	4 (8.2)
Statin	37 (75.5)
ASA	
1	2 (4.1)
2	32 (65.3)
3	15 (30.6)

Table 1. Incidence of cardiovascular risk factors of patients presenting with an occluded endograft. AP = angina pectoris; ASA = American Society of Anesthesiologists; CVA = cerebrovascular accident; MI = myocardial infarction; TIA = transient ischemic attack.

Prior to the initial procedure 3 patients (6.1%) had already undergone balloon angioplasty of the SFA without stent placement, and 5 patients (10.2%) had undergone angioplasty of the iliac artery with (n=3) or without (n=2) bare metal stent placement. Two patients were treated for an abdominal aneurysm with an endograft and one had undergone an endarterectomy of the ipsilateral proximal SFA.

Initial procedure

Before the initial procedure the Rutherford category was 3 in 38 patients (77.6%), category 4 in 9 patients (18.4%), category 5 in 1 patient (2%) and category 6 in another patient (2%). The mean maximum walking distance for patients with disabling claudication was 143 ± 91 meters. Before treatment, mean ABI in rest was 0.66 ± 0.19 and after exercise 0.39 ± 0.15. Two lesions (4.1%) were classified as TASC II A lesions, 14 (28.6%) as TASC II B lesions, 14 (28.6%) as TASC II C lesions and 19 (38.7%) as TASC II D lesions. The mean lesion length of the SFA was 13.4 ± 10.0 cm and in 5 patients (10.2%) there was a flush

occlusion of the SFA. Other lesion characteristics are shown in table 2.

	Prior to endograft failure N=49	Post-failure N=49	P-value
ABI	N=47 0.66±0.19	N=18 0.48±0.16	0.002
Rutherford Classification 1 2 3 4 5 6	N=49 0 0 38 (77.6%) 9 (18.4%) 1 (2%) 1 (2%)	N=49 3 (6.1%) 14 (28.6%) 18 (36.7%) 7 (14.3%) 4 8.2%) 3 (6.1%)	0.328
Level patent popliteal artery P1 P2 P3 Occlusion	N=47 37 (75.5%) 9 (18.4%) 1 (2%) 0	N=45 26 (53.1%) 8 (16.3%) 2 (4.1%) 9 (18.4%)	0.001
Anterior tibial artery Open Open with stenosis Occluded	N=48 31 (63.3%) 7 (14.3%) 10 (20.4%)	N=42 22 (44.9%) 6 (12.2%) 14 (28.6%)	0.13
Posterior tibial artery Open Open with stenosis Occluded	N=48 37 (75.5%) 5 (10.2%) 6 (12.2%)	N=42 27 (55.1%) 4 (8.2%) 11 (22.4%)	0.03
Peroneal artery Open Open with stenosis Occluded	N=47 34 (69.4%) 5 (10.2%) 8 (16.3%)	N=42 30 (61.2%) 3 (6.1%) 9 (18.4%)	0.57

Table 2. Clinical outcome prior to endograft placement versus post-failure of patients presenting with an occluded endograft. ABI = ankle brachial index

During the initial procedure, a concomitant endarterectomy of the common femoral artery was performed in three patients (6.1%), of the external iliac artery in two patients (4.1%), of the proximal SFA in one patient (2.0%) and of the deep femoral artery in another patient (2.0%). Angioplasty of the popliteal artery was performed in four patients (8.2%).

In 25 patients (51%) only one endograft was used, while 15 patients (30.6%) were treated with two endografts, 6 patients (12.3%) with three endografts and in three patients (6.1%) four endografts were used. In the vast majority (93.9%) a 6 mm endograft was used. One patient was treated with a 5 mm endograft and the remaining two patients were treated with a 7 mm endograft. Thirty-seven patients (75.5%) were treated with a regular endograft, while the remaining 12 patients were treated with a heparin-bonded endograft (24.5%).

After the procedure, 30 patients (61.2%) were treated with dual anti-platelet therapy, 8 patients (16.3%) received acetylsalicylic acid 80mg and one patient (2%) was treated with clopidogrel 75mg only. Six patients (12.2%) were treated by coumarin derivates because of other indications of which two received also acetylsalicylic acid. Of the remaining 4 patients (8.2%) postoperative medication could not be retrieved. Seventy-four percent of patients (n=36) were treated with statins. After the initial procedure, a clinical improvement was observed in all but one patient. This patient had an early occlusion and was treated with chemical thrombolysis. The ABI was significantly increased to 0.95 ± 0.26 ($p<0.001$). The 30-day morbidity was 8.2% (n=4), and included wound infection (n=1), hematoma (n=1), decubitus (n=1) and a deep vein thrombosis (n=1). During the first year after the initial procedure 15 of 49 patients (30.6%) that finally failed had already an occlusion of the endograft, that was successfully treated by surgical thrombectomy (n=1) or chemical thrombolysis (n=14). Eleven patients underwent an additional angioplasty of the SFA or popliteal artery with (n=4) or without (n=7) additional stent placement and in 2 patients a toe amputation was performed.

Outcome of failures

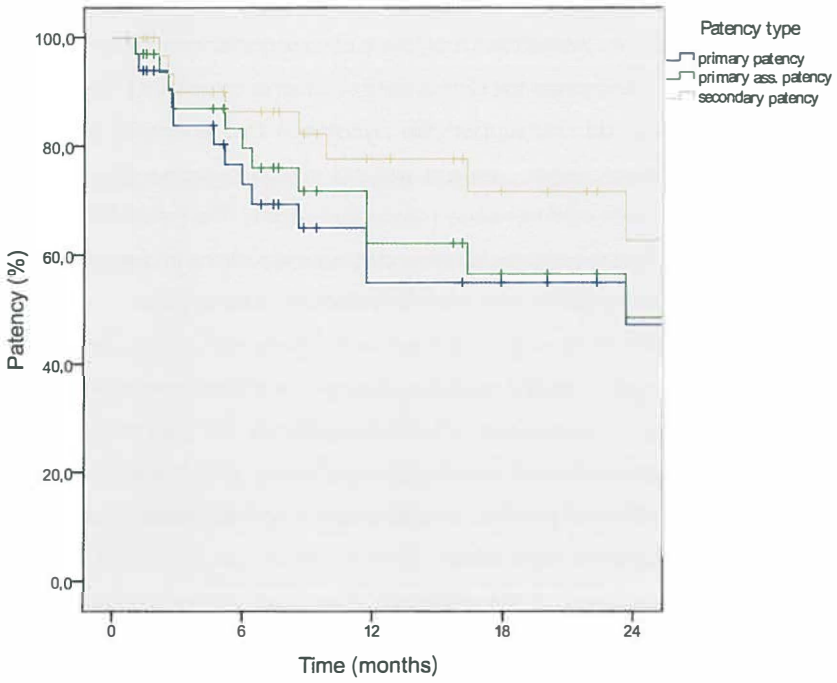
The median time from initial surgery to failure was 7.3 months (range 0.4-74.4 months). Six endografts failed within the first 30 days, 23 others within the first 6 months and another 7 within the first year after treatment. The remaining endografts failed at 18 months (n=4), 28 months (n=4), 32 months (n=2), 43 months (n=2) and 74 months (n=1). The Rutherford categories of these patients after failure are depicted in table 2. The overall clinical state after endograft failure did not significantly differ from the clinical state before the initial procedure (3.1±1.3 vs. 3.3±0.6, respectively, p=0.33). Of the 49 patients 21 (42.9%) presented within the same Rutherford category, 18 (36.7%) with an improved category and 10 (20.4%) with a deteriorated category. The maximum walking distance

after failure was recorded in 22 patients (44.9%). Nineteen patients (38.8%) had a mean maximum walking distance of 158 ± 127 meters, which was not significantly different from their maximum walking distance before the initial procedure (p=0.69). Three others (6.1%) had an unlimited walking distance. Univariate analysis of cardiovascular risk factors did not show any significant correlation with clinical state after failure. The mean ABI after failure was significantly lower than the ABI before the initial procedure (p<0.01). However, the post-failure ABI was often missing. When comparing the index ABI with the post failure ABI in the 18 patients with an known post-failure ABI the difference was still significant (0.64 ± 0.14 vs. 0.48 ± 0.16, respectively, p<0.01). At time of failure, the level at which the popliteal artery was patent was significantly more distally, compared to before baseline (p<0.001).

Twelve patients (24.5%) with a failed endograft were treated conservatively and 37 patients (75.5%) underwent a secondary reconstruction . The median follow-up of the conservatively treated group was 9.9 months (range 0.4-36.4 months). The maximum walking distance in this subgroup varied from 1000 meters to an unrestricted walking distance. All patients of the conservative group were discharged from further follow-up and were categorized as Rutherford 1.

The median follow-up after secondary surgery was 7.5 months (range 0.7-100.2 months). In 34 patients (69.4%) a secondary bypass was constructed. In 22 of them (44.9%) an AK femoro-popliteal bypass was constructed with either vein (n=9) or prosthetic material (n=13). Twelve patients (24.5%) were treated with a below-knee (BK) bypass with either vein (n=9) or prosthetic material (n=3). At 1 year, the primary patency was 55.1%, the primary-assisted patency was 62.3% and the secondary patency was 77.7% (Fig. 1). Re-interventions of the secondary bypass were performed in 8 patients (36.4%) with an AK bypass and in 5 patients (41.7%) with a BK bypass, including angioplasty (n= 5), chemical thrombolysis (n=1) and surgical thrombectomy (n=2). In 3 patients a third bypass was constructed, all BK. In total two of 49 patients (4.1%) underwent a below-knee amputation, one after unsuccessful chemical thrombolysis due to endograft failure and one after failure of the secondary procedure. The patient with an unsuccessful chemical thrombolysis had an infected hematoma in the lower leg, possibly due to thrombolytic treatment and underwent a below-knee amputation 7 days after bypass surgery. The other patient suffered from a wound infection of the foot after receiving an AK prosthetic bypass and underwent a below-knee amputation 3 months after secondary surgery. Both

patients were diabetic and presented initially with Rutherford category 3, and returned with category 3 and 6, respectively, at time of endograft failure. Amputations were performed 0.2 and 39 months after failure of the endograft, respectively.



Limbs at risk					
Primary patency	34	20	11	9	6
Primary assisted patency	34	22	13	9	6
Secondary patency	34	24	16	11	7
Patency (%)					
Primary patency	100	73.1	55.1	55.1	47.2
Primary assisted patency	100	79.7	62.3	56.6	48.5
Secondary patency	100	86.4	77.7	71.7	62.8
SE (%)					
Primary patency	0	8.2	10.1	10.1	11.3
Primary assisted patency	0	7.4	9.7	10.4	11.6
Secondary patency	0	6.3	8.2	9.5	11.8

Figure 1. Kaplan-Meier curve showing primary, primary-assisted and secondary patency after secondary surgery.

Discussion

The major drawback of using endografts for occlusive arterial disease is considered to be the potential occlusion of collateral arteries, as this may worsen clinical outcome in case of failure. In the present study we have shown that failure of endografts, inserted for occlusive disease of the SFA, does not deteriorate the clinical state of patients compared to the baseline situation. The data therefore do not support the hypothesis that endograft placement, possibly covering collateral circulation, worsens patients clinical outcome after failure. Seventy-six percent of patient with a failure needed secondary surgery. The theory that the use of covered stents does not affect the options for secondary reconstructions in case of failure could not be confirmed as 25% of patients with a failure ended with a BK bypass.

Data of the present study may contribute to the discussion on the place of endografts in the treatment algorithm of SFA occlusive disease. It has been thought that endografts may postpone surgery in this category of often frail patients and may be a 'bridge to surgery'. In the present study we found that after a mean follow-up of 2 years no secondary surgery was indicated in 89% of patients due to patency of the bypass or due to the fact that there was no indication after failure. Almost 25% of our population had no remaining symptoms after occlusion of the endograft. The observation that 80% of patients do not show deteriorated clinical outcome after failure and may even improve suggests that the covering of collaterals may not be clinically relevant in this group of patients. This, however, may not be extrapolated to the popliteal artery, which is regularly involved in TASC II D lesions. It seems reasonable to assume that the preservation of collaterals in this area may contribute to the clinical outcome after failure. The use of re-entry devices or the combined antegrade-retrograde approach may contribute to spare as much collaterals as possible at the popliteal level[7].

Surprisingly, although endograft thrombosis was related to a decreased ABI, the clinical state was often similar or even improved when compared to the baseline situation. The reason for this is unknown, but it may be hypotized that a similar phenomenon occurs as is described during walking exercise training, where an increased clinical performance is not related to an increased ABI[8].This emphasizes the discrepancy between clinical state and the ABI that might occur, due to unknown reasons. Possibly the treatment of the occlusion with an endograft, allowing a rapid return to daily activities, had provided the patient sufficient time to develop new collaterals.

In the present study 33% of patients showed a progression of disease in the popliteal artery distally from the bypass after failure. This was reflected by a decreased ABI, while the quality and quantity of crural outflow vessels was not affected, except for the posterior tibial artery. A condition, that may be considered as ongoing disease. Obviously, this may have contributed to the occurrence of failure. Due to this progression a BK bypass was indicated in 1 out of 3 patients, possibly affecting the outcome of the secondary procedure. In half of them prosthetic material was used, mostly because the saphenous vein was unsuitable. This is in line with the observation of Gisbertz et al. that only 45% of patients have a suitable saphenous vein available, as was shown in a randomized trial comparing surgery to remote endarterectomy[9]. The outcome of secondary surgery was rather disappointing in the present study. Although it was a mixed group of AK and BK bypasses, the primary 1-year patency was as low as 55.1%. Nolan et al. recently came to the same conclusion in a retrospective analysis of 1880 lower limb bypasses[10]. They found that prior ipsilateral endovascular revascularization or bypass surgery, but also dialysis dependence, the use of a prosthetic conduit, and distal bypass target were independent predictors of higher 1-year amputation and graft occlusion rates. The high failure rate of secondary procedures might be at dispense of progression of disease and the vulnerability of this specific patient group or due to other risk factors, such as co-morbidity, a poor run-off and type of graft material. In the present cohort no composite or arm vein conduits were used. The sample size of our cohort withheld us from further analysis and conclusions on this point.

Regardless of the fact that secondary surgery is related to a relatively high failure rate the amputation rate was low in our study. The amputation rate was 4% in the group of patients with a failed bypass, but only after failure of a secondary procedure. The amputation rate after failure of the secondary procedure was only 4%, which is much lower than the 31%, as described by Nolan et al. Our data in line with previous reports on the outcome of endografts for occlusive SFA disease which also described low overall amputation rates (0-4%)[5,11,12]. Defining the role of endografts for occlusive SFA disease remains a future challenge since it depends on many variables, including the outcome of failures described here. Besides patency rates, issues like quality of life and cost benefit analysis are also important in the discussion. Hopefully, randomized trials, such as the SUrgical versus PERcutaneous Bypass (SUPERB) trial will provide answers to settle this debate[13].

Limitations of the present study are mainly related to the retrospective analysis of the prospective database. Data were not always complete which may have affected outcome. Moreover, although this is the largest group of failed endografts described to date, the sample size is still relatively small. This renders a sub-analysis to various factors affecting the outcome of failure unreliable. Additional comparative studies are indicated to confirm our data. During the study period the design of the endograft has been changed as the heparin-bonding technology and the contoured edge were introduced. The present study design unfortunately does not allow a comparison between both endografts, since sample sizes are too low.

In conclusion, we have shown that failure endografts is not related to a deterioration of the clinical state in the majority of patients, thereby rejecting the hypothesis that coverage of collateral arteries reduces the limb salvage rate after surgery. Secondary procedures are related to low patency rates, but amputation rates are low.

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4

Chapter 5

Outcome of thrombolysis and thrombectomy for thrombosed endografts inserted in the superficial femoral artery for occlusive disease

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Abstract

Background

The use of endografts for superficial femoral artery (SFA) occlusive disease is matter for debate and the optimal treatment for thrombosed endografts has not been clearly elucidated. The aim was to evaluate the efficacy and outcome of thrombolysis and thrombectomy of thrombosed endografts inserted for SFA occlusive disease.

Methods

Patients treated with a polytetrafluoroethylene endograft between November 2001 and December 2011 were gathered in a database and those that underwent thrombolysis or thrombectomy were retrospectively analyzed.

Results

Seventy-nine patients presented with an endograft thrombosis of which 46 (58%) were treated with thrombolysis (n=40, 87%) or thrombectomy (n=6, 13%). The clinical state was classified as category I in 15 (33%), IIa in 20 (43%) and IIb in 11 patients (24%). Median time from insertion to thrombosis was 3 months (range 0-53 months). Thrombolysis was successful in 38 patients (95%) and the time needed for lysis was 24 hours (range 3-48 hours). Thrombectomy was successful in all 6 patients. Thrombosis without causal lesion occurred more in occlusions that presented <30 days after insertion (p=0.01). The primary, primary-assisted, and secondary patency rates of thrombolysis and thrombectomy at 6 months were 56% and 67%, 56% and 67% and 68% and 67%, respectively. Three patients eventually required a major amputation.

Conclusion

Thrombolysis and thrombectomy of thrombosed endografts in the SFA is effective and safe. Patency rates after treatment are moderate but in two thirds of the patients a prolonged secondary patency can be achieved.

Introduction

The role of endografts in the treatment algorithm of superficial femoral artery (SFA) occlusive disease is still under debate. According to the TASC II guidelines[1], surgical reconstruction is the gold standard for lesions longer than 15 cm in length. Surgery, however, is associated with more complications and a prolonged hospital stay[2]. A randomized trial has shown that with the use of endografts similar patency rates may be achieved as with an above the knee femoropopliteal bypasses up to 4-years follow-up[3]. With the introduction of the heparin-bonding technology the results of endografts may further increase. Recently, we have described a 1-year primary patency of 76%, a primary-assisted patency of 82%, and a secondary patency of 89% in a series of long occlusive lesions of the SFA treated with such endografts[4].

Acute thrombosis often caused by edge stensosis is the most common cause of failure of an endograft, and may lead to limb-threatening conditions. Thrombectomy is an effective treatment modality of acute thrombosed native arteries and bypass grafts, but thrombolysis has developed into an accepted treatment alternative. In a Cochrane review it was shown that to date none of these two modalities can be advocated as initial treatment as there was no overall difference in limb salvage or death at one year between surgery and thrombolysis[5]. In another recent review it was concluded that catheter-directed thrombolysis should be considered a complementary and not a competing technology with surgical revascularization, with an acceptable low complication rate[6].

To date, no studies have been performed focusing on the optimal treatment modality of thrombosed endografts, inserted in the SFA for occlusive disease. The aim of the present study was to evaluate the efficacy and outcome of thrombolysis and thrombectomy of thrombosed endografts that were inserted for SFA occlusive disease.

Materials and Methods

All patients, treated with a polytetrafluoroethylene (ePTFE) covered endograft in three hospitals (Rijnstate Hospital Arnhem, Isala Clinics Zwolle, and Antonius Hospital Sneek, The Netherlands) between November 2001 and December 2011 were prospectively gathered in a database and retrospectively analyzed. Anatomical suitability and preference

of both patient and surgeon were considered before opting for endovascular treatment. Clinical assessment, ankle-brachial index (ABI) measurements and ultrasound scans at 1, 3, 6 and 12 months and yearly thereafter, were aspects of routine follow-up, including the registration of complications and additional treatments in the hospital files. This database was previously used for the analysis of another cohort, focusing on the clinical outcome of patients that presented with a definitive failure of the endograft[7]. Inclusion criteria for the current study were patients that presented with an thrombosed endograft, either during admission or during routine surveillance, and were treated with thrombolysis or thrombectomy. The choice was mostly based on the clinical state of the patient. In case of acute ischemia with muscle weakness and sensory loss surgery was indicated.

Patient demographics, clinical status, medical history were retrospectively analyzed. Additionally, the procedural aspects of the endograft implantation and thrombolysis or thrombectomy, as well as the follow-up after the secondary procedure were gathered. Co-morbidity was scored according to the Society for Vascular Surgery (SVS) and American Association for Vascular Surgery (AAVS) medical co-morbidity scoring system[8]. Clinical symptoms and ABI measurements at the time of the implantation and at the time of occlusion were gathered. The Rutherford classification was used to categorize the clinical symptoms. Characteristics of the lesions were reviewed at the time of the index procedure and scored according to the TASC II criteria[1] and scored additionally at the time of occlusion. Patency of run-off vessels was scored at both time points. The amputation rate and the outcome of secondary procedures were assessed.

Endograft placement

The treatment protocol of endograft placement has been previously described[4]. Briefly, the common femoral artery was approached either percutaneous or surgically. The diseased segment was passed using a Terumo® wire (Terumo Medical Corporation, Elkton, MD, USA) and a catheter. Subsequently a re-entry was created distal from the lesion, the segment was pre-dilated and endografts (Viabahn Endoprosthesis, W.L. Gore & associates, Flagstaff, AZ, USA) were positioned from distal to proximal with minimal oversizing. The entire diseased segment was covered with endografts, which were post-dilated with an angioplasty balloon of the same size as the endograft. Control angiography of the bypass and outflow vessels was performed routinely.

Thrombolysis

Patients underwent a retrograde puncture of the common femoral artery under local anesthesia using the Seldinger technique. Through a 6Fr sheath a thrombolysis catheter (Uni-Fuse™, Angiodynamics, Latham, NY) was inserted into the thrombosed endograft. Then, a bolus of 100.000U medicinase (Abbokinase®, Abbott Laboratories, Chicago, IL) was infused into the thrombus, followed by a continuous infusion of 250.000U/24 h medicinase until complete lysis was achieved. During treatment patients received 25.000U/24h heparin, controlled with repeated APTT measurements, and adapted if necessary. Follow-up angiograms were repetitively made in order to evaluate the progression of thrombolysis. Any detected cause of the thrombosis was treated immediately, according to the local protocols.

Thrombectomy

Surgical thrombectomy was performed under either regional or general anesthesia, by exposure of either the common femoral artery or the popliteal artery. After administration of 5000U of heparin, an arteriotomy was performed and balloon catheters (LeMaitre Vascular, Burlington, MA) were used to extract the clot from the occluded endograft. This was repeated until no more thrombus was extracted. The distal and proximal segment were then flushed with heparin saline and the arteriotomy was closed using a Prolene™ 6.0 (Eticon, Norderstedt, Germany). Imaging of the endograft was always performed per- or post-procedural and any detected cause of the thrombosis was treated according to the local protocols.

Definitions

A thrombosis was defined as absence of flow in the endograft. Successful lysis was defined as clot lysis exceeding 95% of the endograft as determined by digital substraction angiography Primary patency after thrombolytic treatment was defined as the absence of treatment for restenosis or occlusion in a patent endograft after primary thrombolytic therapy. Restenosis was defined as a lesion with a peak systolic velocity (PSV) ratio >2.5, as measured on ultrasound scanning. Primary-assisted patency was defined as patency achieved by secondary endovascular intervention(s) to treat restenosis of the endograft after primary thrombolytic therapy. Secondary patency was defined as the absence of secondary thrombolytic or surgical treatment performed for endograft occlusion in a

patent endograft after primary thrombolytic therapy. A definitive failure was defined as occlusion of the endograft, with or without clinical symptoms, not responding to therapy or not treated due to the absence of clinical symptoms. Major amputation was defined as an amputation above the ankle.

Endpoints

The primary endpoints of the study were the efficacy of thrombolytic treatment for endograft occlusion and the patency rates after treatment. Secondary endpoints included complications, secondary interventions and amputation rate.

Statistical Analysis

Categorical variables are presented as counts and percentages; continuous variables are presented as mean ± standard deviation or as median with range (depending on Gaussian distribution). All analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Kaplan-Meier survival analysis and the log-rank test were performed to assess primary, primary assisted and secondary patency rates after thrombolytic therapy. A two-sided P-value <0.05 was considered statistically significant.

Results

During the study period a total of 341 patients were treated with endografts for SFA occlusive disease. A total of 79 patients had an occlusion of the endograft of which 46 patients (58%) were treated with either thrombolysis (n=40, 87%) or thrombectomy (n=6, 13%). The median age of this group was 66.8 years (range 30-80) and 33 patients (72%) were male. Cardiovascular risk factors of the study population are shown in Table 1.

Patient Characteristics	N (%)
ASA	
1	2 (4)
2	29 (63)
3	15 (33)

Patient Characteristics	N (%)
Tobacco use	
Never, >10 years ago	8 (17)
No, but <10 years ago	8 (17)
Yes <pack/day	17 (37)
Yes >pack/day	10 (22)
Unknown	3 (7)
Hyperlipidemia	
Normal lipids	5 (11)
Mildly elevated, dietary	1 (2)
Type II,III, IV, dietary	0
Treated with drugs	39 (85)
Unknown	1 (2)
Diabetes mellitus	
No	28 (60)
Adult, dietary	9 (20)
Adult, insulin dependent	9 (20)
Juvenile diabetes	0
Hypertension	
No	9 (20)
Treated with one drug	12 (26)
Treated with two drugs	12 (26)
Treated with three drugs	13 (28)
Renal Failure	
No	42 (91)
Creatinin 1.5-3.0 mg/dl ; GFS 30-50 ml/min	2 (4)
Creatinin 3.0-6.0 mg/dl ; GFS 15-30 ml/min	2 (4)
Creatinin >6.0 mg/dl ; GFS <15 ml/min, renal Transplant	0
Pulmonary disease	
Asymptomatic	42 (91)
Mild dyspnoe	3 (7)
Moderate dyspnoe	1 (2)
O2-needed, pulmonary hypertension	0
Cardiac status	
Asymptomatic	26 (57)
Non recent MI (>6m), or asymptomatic MI on ECG	14 (30)
Stable AP, arrhythmias, treatable heart failure	5 (11)
Instable AP, recent MI (<6m)	1 (2)
Carotid status	
No disease	34 (74)
Asymptomatic, signs of disease	1 (2)
TIA/stroke without rest symptoms	10 (22)
TIA/stroke with rest symptoms	1 (2)

Table 1. The incidence of cardiovascular risk factors of patients presenting with a thrombosed endograft treated with thrombolysis or thrombectomy.

The indication for insertion of the endograft(s) was Rutherford category 3 in 34 patients (74%), category 4 in 6 patients (13%), category 5 in 5 patients (11%) and category 6 in one patient. The mean ABI before endograft insertion was 0.65 ± 0.17, and after exercise 0.39 ± 0.15. Lesions were categorized as TASC II A in 2 patients (4%), as TASC II B in 8 patients (17%), TASC II C in 12 patients (26%) and TASC II D in 23 patients (50%). The mean treated lesion length was 17.2 ± 10.9 cm. Other lesion characteristics are depicted in Table 2.

Length diseased segment (cm)		17.2 ± 10.9
Diameter proximal SFA (mm)		4.5 ± 1.2
Flush occlusion SFA		11 (23.4%)
Diameter popliteal artery (mm)		3.9 ± 1.2
Level patent popliteal artery		
P1		32 (68.1%)
P2		13 (27.7%)
P3		0
Outflow crural vessels		
Posterior tibial artery	open; open with stenosis; occluded	31 (66%); 5 (10.6%); 8 (17%)
Anterior tibial artery	open; open with stenosis; occluded	27 (57.4%); 5 (10.6%); 12 (25.5%)
Peroneal artery	open; open with stenosis; occluded	35 (74.5%); 5 (10.6%); 4 (8.5%)

Table 2. The lesion characteristics of patients presenting with a thrombosed endograft treated with thrombolysis or thrombectomy, prior to the endograft implantation.

In 17 patients (37%) one endograft was used, in 15 patients (32%) two endografts, in 9 patients (20%) three endografts, and in the remaining 5 patients (11%) four endografts. The majority of patients (85%) were treated with a 6 mm endograft. The remaining patients were treated with either a 5 mm endograft (n=2) or with a 7 mm endograft (n=5). Twenty-one patients (46%) were treated with a regular endograft and 25 patients (54%) were treated with a heparin-bonded endograft, based on the timeframe of their treatment. A concomitant endarterectomy of the common femoral artery was performed in 4 patients (9%).

Endograft thrombosis

The median time from insertion to primary thrombosis was 3 months with a range of 0-53 months. The vast majority (89%) of thrombosis occurred within the first year after insertion

of the endograft(s) of which 17 within the first 30 days (37%). At the time of thrombosis the clinical state was classified as category I in 15 patients (33%), category IIa in 20 patients (43%) and category IIb in 11 patients, according to the Rutherford classification for acute limb ischemia[7]. The mean ABI at the time of occlusion was 0.54 ± 0.23. The median time from clinical symptoms until thrombolytic therapy and thrombectomy was 0 days (range 0-6 days) and 0 days (range 0-15 days), respectively. Comparing the difference in risk factors between patients undergoing thrombolytic therapy versus thrombectomy showed nearly the same percentages in smoking, hypertension, diabetes, cardiac status, carotic status, hyperlipidemia and pulmonary state. Comparison of the clinical state between the two groups showed 67 % patients of the thrombectomy group had an Acute Rutherford I category and 33% an Acute Rutherford IIb. In the thrombolytic group 28 % had an Acute Rutherford category I, 48% category IIa and 23% a category IIb.

Thrombolysis

Complete lysis was achieved in 38 of 40 patients (95%). The median time taken for lysis was 24 hours, with a range of 3-48 hours. In 2 patients additional mechanical thrombolysis was performed using a Hydrolyser™ (Cordis®, Waterloo, Belgium).

After lysis, a significant lesion was found of the proximal edge in 16 patients, and was treated by angioplasty (n=13), angioplasty with stenting (n=2) or extension of the endograft with an additional endograft (n=1). A focal edge stenosis of the distal part of the endograft was found in 12 patients. They were treated with angioplasty (n=10) and/or extension of the endograft with an additional endograft (n=2). Other causal lesions included in stent stenosis (n=2) which were both treated with angioplasty.

No causal stenosis of the endograft or the in- or outflow vessels was found in 9 patients (22%). Overall, in the group that presented <30 days after insertion of the endograft significantly more patients had no causal stenosis compared with patients that presented at a later stage (47% vs. 14%, respectively, p=0.01). One patient died before any causal lesion could be identified.

Twenty-three patients (58%) had an outflow with 3 vessels after thrombolysis, 10 patients (30%) had a 2 vessel outflow, 5 patients (13%) had an one vessel outflow and one patient (3%) had no outflow vessels. The one patient with no outflow vessels had an unsuccessful thrombolysis and developed an infected hematoma in the calf and eventually required an above the knee amputation.

Complications occurred in 7 patients (18%) and included two conservatively treated groin hematomas, one pneumonia, one wound infection at the puncture site and two patients had a temporary paresis of the peroneal nerve as part of a reperfusion syndrome. No compartment syndromes were identified. One patient died during thrombolytic therapy due to an unknown cause. Unfortunately, no autopsy was performed to determine if cause of death was related to the thrombolysis. The median length of stay in the medium care unit was 1 day (range 0-2 days) and the median length of hospital stay was 5 days (range 2-19 days).

Post-procedurally, 30 patients were treated with acetylsalicylic acid 80 mg, in 4 patients (10%) combined with dipyridamol 75 mg, in 16 others (40%) combined with clopidogrel 75 mg and in 6 patients (15%) combined with warfarin derivates. Six patients (15%) were treated with the combination of clopidogrel 75 mg and warfarin derivates, and three (8%) patients were treated with warfarin derivates only. Thirty-eight patients (95%) were on statin treatment.

Thrombectomy

The median duration of thrombectomy was 90 minutes (range 55-136 minutes) and the procedure was successful in all patients (100%). In one patient (17%) an additional angioplasty of the anterior tibial artery, and in 2 patients (33%) a concomitant endarterectomy of the common femoral artery was performed. No causal stenosis of the endograft was found in 2 of 6 patients (33%). Complications occurred in 3 patients and included conservatively treated groin hematoma (n=2) and one re-bleeding requiring surgery. After thrombectomy, three patients (50%) had a 3 vessel outflow, 1 patient (17%) had an outflow with 2 vessels and 2 patients (33%) had an outflow with one vessel. The median length of stay of the thrombectomy group was 7 days (range 4-18 days).

Postoperatively, 4 patients received acetylsalicylic acid 80 mg; in 2 patients (33%) combined with persantin 75 mg and in 1 patient (17%) combined with clopidogrel 75 mg. One patient (17%) was treated with the combination of warfarin derivates and clopidogrel 75 mg and one patient (17%) was treated with warfarin derivates only. All 6 patients were on statin treatment.

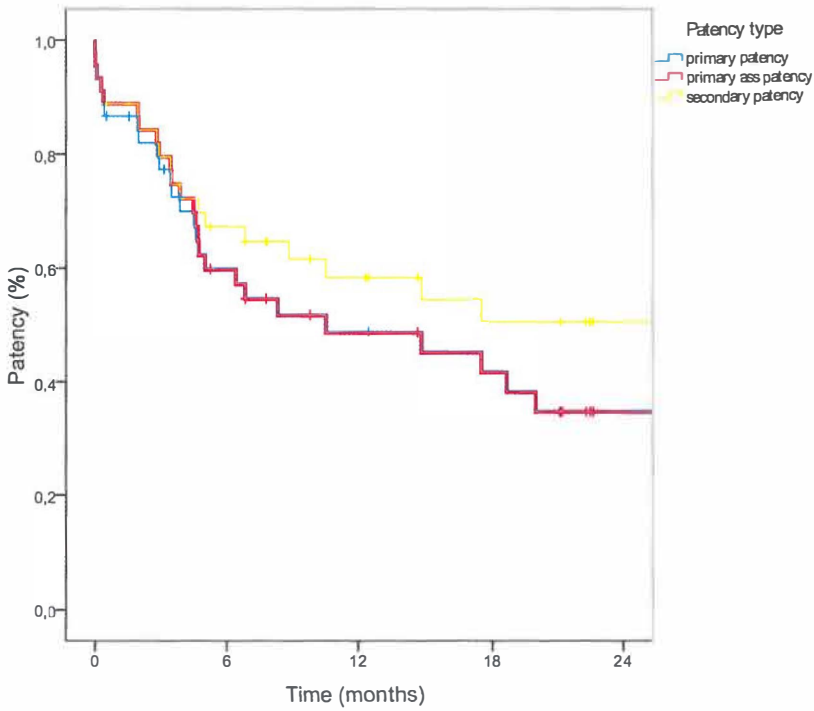
Follow-up after primary thrombolysis or thrombectomy

The median follow-up period after thrombolysis or thrombectomy was 14 months (range 1-69 months). The median ABI after thrombolytic treatment was 0.96 (range 0.28-1.18).

All patients, except one, showed clinical improvement during the first month. Twenty-five patients (56%) were categorized as Rutherford 1, 8 patients (18%) as Rutherford 2, 2 patients (4%) as Rutherford 3, 2 patients (4%) as Rutherford 4, 3 patients (7%) as Rutherford 5 and one patient (2%) as Rutherford 6. The one patient who showed no clinical improvement had an unsuccessful primary thrombolysis and developed an infected hematoma in the calf, as mentioned above. The comparison in Rutherford category of different moments is shown in figure 1. Comparing the clinical state in Rutherford post endograft versus post thrombolysis 38% had the same Rutherford, 41 had a improved category and 19% had a detoriated category. Of 8 patients either the post endograft Rutherford category or the post thrombolysis Rutherford category was missing.The clinical state comparison in Rutherford of post endograft versus post thrombectomy showed 60% with the same Rutherford category, 20% with an improved category and 20% with a detoriated category. Of one patient the post endograft Rutherford data was missing. The median Rutherford category pre-endograft insertion, post-endograft insertion, at occlusion and after thrombolytic therapy was 3 (range 1-6), 1 (range 1-6), 4 (range 2-6) and 1 (range 1-6), respectively.

The overall primary, primary assisted and secondary patency rates after primary thrombolytic therapy are shown in figure 1. The primary, primary-assisted, and secondary patency rates of thrombolysis at 6 months were 56%, 56% and 68%, respectively and those of thrombectomy 67%, 67% and 67%, respectively.

During the follow-up period re-interventions were performed in 12 patients (26%) and included plain balloon angioplasty (n=10) of the SFA (n=4), the proximal edge (n=3), the distal edge (n=2) and the popliteal artery (n=1). An angioplasty with stent placement was performed in two patients in the SFA and popliteal artery, respectively. Due to a re-occlusion, secondary thrombolysis was performed in 10 patients and thrombectomy in 4 patients. All re-interventions were performed within the first 18 months after the first thrombolytic treatment.



Limbs at risk					
Primary patency	45	23	16	12	6
Primary assisted patency	45	23	16	12	6
Secondary patency	45	26	18	14	9
Patency (%)					
Primary patency	100	60.0	48.8	41.8	34.9
Primary assisted patency	100	59.8	48.7	41.7	34.8
Secondary patency	100	67.2	58.3	54.4	50.6
SE (%)					
Primary patency	0	7.6	8.0	8.2	8.2
Primary assisted patency	0	7.6	8.0	8.2	8.2
Secondary patency	0	7.2	7.9	8.3	8.6

Figure 1. Primary, primary-assisted and secondary patency rates after thrombolytic treatment of a thrombosed endograft, inserted in the superficial femoral artery for occlusive disease.

During follow-up, a definitive failure occurred in 16 patients (36%), of which 2 were initially treated by thrombectomy (13%). In total, 4 patients (25%) with a definitive failure were treated conservatively, because they had no or only minor clinical symptoms. The remaining 12 patients were treated with bypass surgery. In 4 patients an above the knee femoropopliteal bypass was created, 2 with a venous conduit and 2 with prosthetic material. The remaining 8 patients were treated with a below the knee femoropopliteal bypass, 5 with a venous conduit and 3 with prosthetic material, all due to the absence of suitable vein.

During follow-up, three of the 45 patients that were treated with thrombolysis or thrombectomy eventually underwent a major amputation (7%). The first patient has been mentioned above, a second patient, that was treated with thrombectomy, developed acute limb ischemia 3 months after secondary thrombolysis and in the third patient a failure of the above the knee prosthetic bypass occurred. He was treated with a below the knee bypass and subsequently developed a progressive infection of the foot. Two patients presented initially with Rutherford 3 and one patient with Rutherford 4. The amputations were performed 1, 9 and 39 months after primary thrombosis, respectively.

Discussion

In the present study we have shown that thrombolysis and thrombectomy are both safe treatment modalities for the treatment of thrombosed endografts inserted in the SFA for occlusive disease. Technical success rates are high and major complication and amputation rates are low. Patency rates after successful treatment of thrombosed endografts seem to be lower than those described after initial placement[4,9]. However, the patency rates are within range of patency rates after thrombolysis described in literature that vary between 38 and 90%[6]. Yet, in two thirds of our patients prolonged secondary patency could be achieved and bypass surgery excluded, or at least postponed.

In our study, 53% of patients required an additional treatment after thrombolysis consisting of a PTA with or without additional stenting or stentgrafting. In 60% of cases an edge stenosis was the underlying cause of occlusion, emphasizing the urge for strict follow-up and early treatment of edge stenosis. Most of the edge stenosis were treated with plain balloon angioplasty. Within the paradigm of covering the entire diseased segment an extension of the endograft appears to be the most appropriate choice. Nevertheless, in proximity of collaterals plain balloon angioplasty may be a valid option, while the effects of drug eluting balloons remain to be studied. Further studies should focus on the optimal treatment modality of edge stenosis.

Overall, no causal lesion could be identified in 24% of patients and this was significantly more the case in patients that presented with an occlusion <30 days after insertion of the endograft(s). In those patients no causal lesion could be identified in half of the cases. Analysis of possible risk factors of failure did not show any significant association, especially

not in the used anticoagulation or the occurrence complications. Several studies found confounding factors which influence the success rate of thrombolysis, such as diabetes, a history of lower limb ischemia, an occluded bypass graft and poor runoff[10-13]. Obviously the groups, as described in the present analysis, may well have been too small to identify such a relation. Moreover, an occlusion without an anatomical cause may also be caused by prolonged flexion of the knee during sleep or activities. This appeared to be the case in some of our patients, but these associations are difficult to prove. Sizing is likely to be amongst the most important factors that could influence the incidence of edge stenosis and subsequent thrombosis. Additional studies on this subject are warranted.

In our study, the vast majority of patients were treated with thrombolysis. We could not identify a difference in outcome between patients treated with thrombolysis and those with thrombectomy, but obviously the group of patients treated with thrombectomy is too small to draw any conclusions. After successful thrombolysis a completion angiogram allows a distinct determination of the vascular tree and possible underlying causes of endograft failure. Additionally, it has been reported that thrombolysis results in more patent outflow vessels compared with thrombectomy[14]. Therefore endovascular thrombolysis could be the preferred treatment modality, especially in the often frail group of patients, with multiple comorbidities[15,16].

Importantly, the clinical state of the patients who needed secondary thrombolytic therapy did not worsen in comparison with the primary thrombolysis. In 64% of patients the Rutherford categorization was equal to primary occlusion while the remaining 2 patients had a even better clinical state compared to primary occlusion. Although the overall complication rate of our series seems high (22%), most of them were minor and self-limiting. In contrast to other studies where they reported major hemorrhagic complication rates varying from 4-13%[11,17,18] our major hemorrhagic rate was low. Only 1 patient (2%) encountered significant bleeding which required surgery. Whether the death of one patient during thrombolysis was caused by bleeding cannot be concluded, as no post-mortal study was performed. These observations support the hypothesis that thrombolytic therapy can always be considered, as secondary failure does not worsen clinical status of the patient.

Various studies have reported amputation rates after thrombolysis of 18-25%[16,19]. In our study, the amputation rate was only 7%. Two amputations occurred after failure of the secondary procedure, one after secondary thrombolysis and one after secondary bypass.

The low amputation rates might be partially explained by the relatively low percentage of patients primarily treated for critical ischemia. Still, the low amputation rates after endografting of the SFA are supported by other studies[7,9,20]. These data provide circumstantial evidence that the overstenting of collaterals in the SFA does not inevitably lead to an endangered limb in case of occlusion.

Limitations of the present study are mainly related to the retrospective design of the data. Furthermore the sample size of our cohort withheld us of further subanalysis. Therefore additional comparative studies are indicated to confirm our data. Discrepancies were seen between the hospital centers in the post-thrombolytic anticoagulation strategy. To date, clear evidence-based guidelines on the anticoagulant therapy after thrombolytic treatment are lacking and therefore future research on this topic is necessary[21,22].

In conclusion our study has shown that an occlusion of an endograft, inserted in the SFA for occlusive disease, may be well treated with thrombolytic therapy with a low rate of major hemorrhagic events and low amputation rates. Patency rates seem to be lower compared to those after insertion, but are in line with those as described after thrombolysis of surgical bypasses.

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Chapter 6

The use of endografts to create an endoluminal femoropopliteal bypass after failed above knee femoropopliteal open bypass surgery

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Abstract

Aim of study

Redo femoropopliteal bypass surgery is associated with increased morbidity, while results of secondary procedures are related to a poor outcome. An endovascular strategy, using endografts, might provide a minimal invasive alternative avoiding the dissection of a previously operated groin.

Materials and Methods

All patients treated with a polytetrafluoroethylene (ePTFE) covered stent for superficial femoral artery occlusive disease between February 2009 and September 2011 were prospectively gathered in a database. Demographics, clinical status, medical history, procedural aspects and follow-up data were retrieved.

Results

A total of 74 patients were included in the database of which five (7%) had been treated with a surgical femoropopliteal bypass before. The indication for intervention was Rutherford category three in all patients and the median ankle-brachial index (ABI) was 0.68.The lesions were classified as TASC II C (n=1) and D (n=4). Technical success was achieved in 100% of cases and the postoperative course was uneventful in all patients. The median ABI had increased to 0.95. After a median follow-up period of 18 months, 4 out of 5 endografts remained patent. Due to a good clinical condition the patient with a failed endoluminal bypass was not re-operated.

Conclusion

The creation of an endoluminal bypass using endografts after failed femoropopliteal bypass surgery is feasible and safe and could be used to avoid or minimize the difficult and hazardous dissection of a previously operated area.

Introduction

According to the Inter-Society Consensus for the management of peripheral arterial disease (TASC II), open bypass surgery is considered the gold standard for long occlusive lesions in the superficial femoral artery (SFA)[1]. A review of the literature has shown that the primary patency rate of venous femoropopliteal bypasses is 81% at two years and 69% at five years, respectively, while results of prosthetic bypasses are inferior[2,3]. At five years, 7-20% of venous bypasses and 17-40% of the PTFE bypasses have definitively failed[4,5]. Results of thrombectomy and thrombolysis aimed to salvage these bypasses are poor. In a series of salvage procedures, including surgical thrombectomy and thrombolysis, Pedersen et al reported a primary patency rate of redo procedures of 32% at three months, 28% at six months and 12% at 12 months[6]. Secondary femoropopliteal bypass surgery is associated with increased morbidity, including wound infection, lymphatic obstruction, lymphorrhea, and neurovascular injury. In a recent study, te Slaa et al. have shown that redo peripheral bypass operations result in significantly more postoperative edema than a first-time performed operation[7].

In order to both improve long-term patency rates of secondary procedures and avoid the dissection of a previously operated groin, thereby possibly reducing the incidence of complications, alternative strategies may be indicated. An endovascular approach using endograft(s) provides a minimally invasive alternative. In a recent publication, McQuade et al. have shown that a primary endoluminal bypass, using ePTFE-covered stents, has patency rates comparable with above knee prosthetic grafts at 4-years follow-up[8]. In secondary open bypass surgery prosthetic grafts are often used because the saphenous vein frequently has been used during the first procedure. The use of endografts for the creation of an endoluminal bypass as a secondary procedure has not been described to date. In this paper we describe the feasibility of an endovascular approach using endograft(s) after failed above knee femoropopliteal bypass surgery.

Materials and Methods

All patients with peripheral arterial disease and treated with a polytetrafluoroethylene (ePTFE) covered stent between February 2009 and September 2011 were prospectively

gathered in a database. In all patients secondary risk prevention was performed according to the national guidelines and all patients with intermittent claudication were initially treated with (supervised) walking exercise. Only those with unsuccessful exercise training were indicated for intervention. The indication for endovascular treatment was based on anatomical suitability and the preference of both patient and surgeon. Generally, covered stents were used in lesions with a length of more than 15 cm, while bare metal stents were used in shorter lesions. Anatomical suitability consisted of an adequate inflow without a flow-limiting stenosis in the aorto-iliac arteries, a patent popliteal artery above the P3 level with a diameter of at least 4.2 mm and at least one patent crural vessel.

Demographics, clinical status and medical history were noted. Procedural aspects and follow-up data were retrieved. Lesions were reviewed and scored according to the TASC II criteria[1]. Additionally lesion length, luminal vessel diameters, and the number of patent run-off vessels were scored.

Follow-up consisted of clinical assessment and duplex ultrasound scans at 1, 3, 6 and 12 months. Complications and additional treatments were registered in the hospital files.

Restenosis was defined as a peak systolic velocity (PSV) ratio >2.5, as measured on ultrasound. An occlusion was defined as absence of flow in the treated segment of the superficial femoral artery.

Treatment protocol

Procedures were performed using antibiotic prophylaxis with cephazolin 1000 mg intravenously. The common femoral artery was approached percutaneously using ultrasound-guided or surgically, in an antegrade fashion according the surgeons' preference. When there was a concomitant lesion in the common or profunda femoral artery an endarterectomy was performed. Heparin (5000 IU) was administered. The diseased segment of the SFA was passed using a Terumo® wire (Terumo Medical Corporation, Elkton, MD) and a catheter, either endoluminal or subintimal, and a re-entry was created distally. The segment was pre-dilated with a regular angioplasty balloon and the endografts were positioned from distal to proximal with minimal oversizing. The entire diseased segment was covered with endografts and endografts were postdilated with an angioplasty balloon with the same size as the endograft. Control angiography of the bypass and outflow vessels was performed routinely. In case of a percutaneous approach, the access was closed using a closure device (Angio-Seal™, St Jude Medical, MN).

The used endograft was the heparin-bonded Viabahn Endoprosthesis (W.L. Gore & associates, Flagstaff, AZ), which is a self-expanding helical nitinol stent covered with a heparin-bonded thin ePTFE tube.
After the procedure patients received statin treatment and dual anti-platelet inhibitors for 1 year, unless oral anticoagulation was indicated for other reasons.

Results

During the study period a total of 74 patients were treated with ePTFE-covered stents for SFA occlusive disease. Results from the RHA cohort have been described recently[9]. Five (7%) patients that had been treated before with an ipsilateral surgical bypass were identified. Four of them were male and one female. The median age was 60 years (range 52-74 years). Cardiovascular risk factors included smoking (3/5), hypertension (4/5), dyslipidemia (3/5), diabetes mellitus (4/5) and cardiac history (4/5). One patient had undergone a kidney transplantation and the median glomerular filtration rate was 72 mL/min (range 63-87 mL/min).
Saphenous vein was used for the initial femoropopliteal reconstruction in three patients and a synthetic conduit in 2. The distal anastomosis was always in the above-knee area. Three bypasses were left-sided and 2 right-sided. The median time frame between initial femoropopliteal reconstruction and failure was 4.8 years (range 0.3-10.2 years). In 4 patients the entire bypass was occluded and in the remaining patient there was an occlusion of the popliteal artery immediately below the distal anastomosis, requiring reintervention.
The indication for intervention was Rutherford category three in all patients and the median ankle-brachial index (ABI) was 0.68 (range 0.46-0.85).The lesion was classified as TASC II C (n=1) and D (n=4). The median lesion length was 34 cm (range 8-38 cm) and the diameter of the popliteal artery was 5.5 mm (range 5.2-6.0 mm). The popliteal artery was patent above the upper border of the patella (P1) in three patients and below the tibial plateau (P3) in two. In two patients the SFA was occluded flush from the origin. Three patients had three and two patients had two crural outflow vessels.
Two patients were operated using general anesthesia, two using regional anesthesia and in one patient only local anesthesia was used. The use of spinal or general anesthetics

enabled a conversion to a surgical bypass within the same session, in case of a technical failure of the procedure. Three patients were treated percutaneously, and in two patients the common femoral artery was dissected. In one of them an additional endarterectomy with patch was performed. In all patients the passage was subintimal without using re-entry devices, and in all patients the endografts (heparin-bonded Viabahn Endoprosthesis, W.L. Gore & associates, Flagstaff, AZ) were successfully inserted. In 1 patient 1 endograft was used, in two patients two endografts and in the remaining two patients three endografts with a diameter of 6 mm (n=4) and 7 mm (n=1). The median operation time was 76 minutes (range 60-180 minutes), the used contrast medium 105 mL (range 80-195 mL) and the fluoroscopy time was 13 min (range 11-14 min).

The postoperative course was uneventful in all patients. Specifically, no wound healing disturbances or postoperative edema occurred. Patients were discharged on the second postoperative day (range 1-5) with the two patients undergoing a hybrid procedure staying longest, respectively three and five days. The median ABI had increased to 0.95 (range 0.70-1.18). The thirty-day morbidity and mortality rates were zero.

Follow-up was available for all patients and the median follow-up was 18 months (range 7-29 months). During follow-up all but one endograft remained patient. One patient needed a thrombectomy for an acute occlusion 40 days after insertion and remained patent afterwards. In one other patient routine duplex control demonstrated an asymptomatic occlusion of the endografts 12-months after insertion. Due to his good clinical condition patient was refrained from re-intervention. The Rutherford classification had increased from category 3, with a walking distance of less than 100m before the procedure to category 2, with a walking distance of 400m after failure. His walking distance further improved following walking exercise. During follow-up there were no minor or major amputations.

Figure 1a and b.

Pre-procedureal angiography from a 57-year old male patient suffering from Rutherfort category three showing a 38 cm long TASC II D lesion of the superficial femoral artery. Patient, with a history of smoking, hypertension and dyslipidemia, had been treated with a venous above-knee femoropopliteal artery 6 years earlier. Arrow pointing at the proximal and distal anastomosis, respectively.

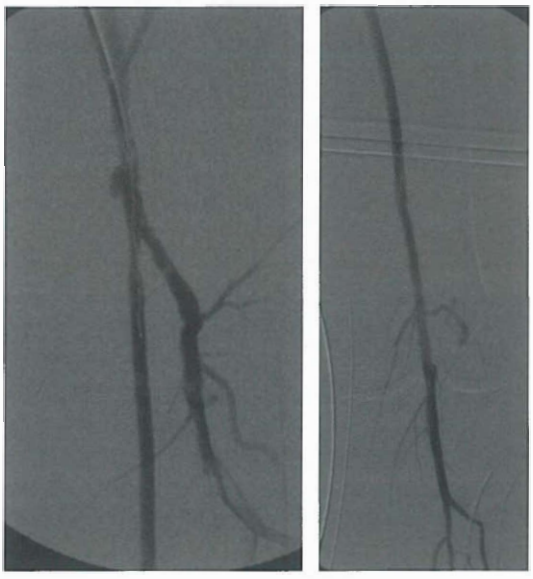

Figure 2a and b.

Post-procedural angiography, after percutaneuous insertion of an endoluminal bypass using three 6mm endografts (15, 15 and 10 cm long heparin-bonded Viabahn Endoprothesis, W.L. Gore & associates, Flagstaff, AZ) showing a patent endoluminal bypass with unaffected outflow vessels.

Discussion

In the present paper we have shown that an endovascular approach using endografts after failed femoropopliteal bypass surgery is feasible and safe for long chronic occlusive lesions of the SFA. Although the present study includes only few patients and follow-up is limited, our data suggest that this strategy could be a valid alternative for redo femoropopliteal bypass surgery. Although larger series would provide a higher level of evidence, the combination of a failed above knee bypass, an indication for re-intervention and a suitable anatomy for endovascular treatment seems to be uncommon. In our series, only 7% of patients treated with an endograft had been previously operated, complicating comparative studies with surgical re-intervention.

In an attempt to reduce postsurgical complications, due to the dissection of a previously operated groin, Ascer et al have suggested a preferential use of the external iliac artery as an inflow source[10]. After a mean follow-up of 14 months, 25 out of 29 popliteal bypasses were patent, while only superficial wound infection occurred at the below-knee popliteal incision. As a minimally invasive alternative, Constanza et al. have studied the results of surgical thrombectomy and transluminal balloon angioplasty for failed above-knee femoropopliteal bypass grafts[11]. In their series, surgical thrombectomy along with angioplasty, however, had an unacceptably high rate of failure and limb loss in patients treated for early (<2 years) bypass thrombosis. Surgical graft revision or redo bypass was recommended to achieve successful revascularization in these patients. In the present study we have successfully treated 5 patients using endografts to create an endoluminal bypass after failed femoropopliteal bypass surgery. There were no postoperative complications and the previously performed surgical procedure did not complicate various steps of the endovascular procedure, including access, subintimal dissection, creation of the re-entry, deployment of the endografts and closure of the puncture site. Their observation supports the hypothesis that an endovascular approach is feasible following previous surgical procedures and emphasizes that the dissection of a previous operated groin could be avoided.

The place of endografts in the algorithm of atherosclerotic disease of the SFA is still under debate. In primary procedures the patency rates are comparable with prosthetic surgical bypasses[8], often used in redo surgery. The technique, however, might also be considered as a bridge to surgery, preserving vein and preventing scar formation, related to increased

morbidity at secondary interventions. On the other hand, it may be considered as a way out for those unfit for surgery or as the technique of choice for those with failed surgery, such as in our patients.

In one of our patients the endograft occluded within the first postoperative year. Due to a good clinical condition, with a Rutherford classification that had increased from category 3 before the procedure to category 2 after failure, no re-intervention was performed, indicating that an endovascular strategy may postpone surgery in an often frail group of patients. Conclusions on the long-term performance of the endoluminal bypass after failed surgery may not be drawn from the present data, due to the small sample size. Patency rates, however, might be lower when compared to primary procedures as seems to be true for surgical bypasses. In a series of 112 prosthetic bypasses, Aune et al. have shown that results of redo procedures are inferior to those of primary procedures[12]. Adequate outflow and diameter of the popliteal artery seem to be important parameters for clinical success of an endovascular strategy. Studies with a larger sample size are indicated to clarify the performance of an endoluminal bypass after failed surgical or endovascular treatment using bare metal stents.

In conclusion, we have shown that the creation of an endoluminal bypass using endografts after failed femoropopliteal bypass surgery is feasible and safe and could be used to avoid or minimize the difficult and hazardous dissection of a previously operated area.

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Chapter 7

The combined ipsilateral antegrade-retrograde approach to insert an endoluminal femoropopliteal bypass

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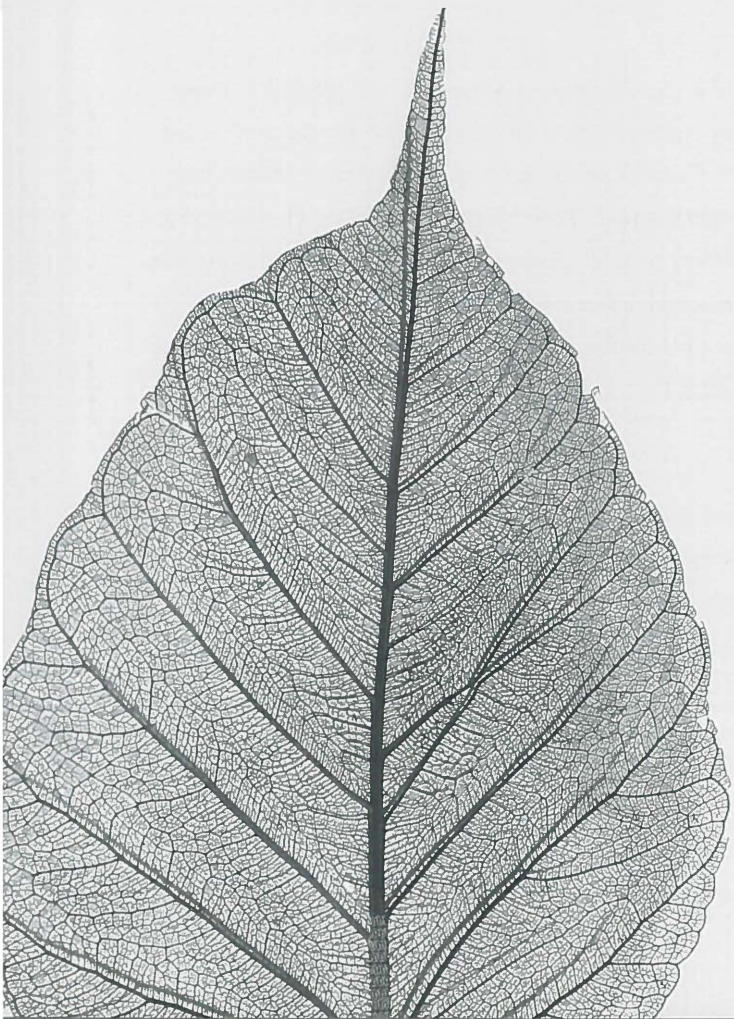

J Vasc Surg 2011;54:1205-1207

Abstract

Introduction

The endoluminal femoropopliteal bypass is a minimally invasive treatment modality for occlusive superficial femoral artery disease. Technical failure of endovascular treatment of chronic total occlusions are often caused by the inability to re-enter the true lumen. Re-entry devices have a high technical success-rate, but increase procedural costs. We describe an alternative technique using an ipsilateral combined antegrade-retrograde approach to insert an endoluminal femoropopliteal bypass.

Technique

In a supine position, with the leg 30-degrees elevated, the popliteal artery is punctured and a 4-french introducer sheath is introduced. The occlusion is crossed from distal to proximal and the wire is advanced through a 6-french sheath that is positioned in the common femoral artery. The occlusion is pre-dilated from proximal and the 're-entry' site is identified on an angiogram. The wire is then withdrawn into the balloon catheter and advanced intraluminally into one of the crural vessels. After confirming the intraluminal position of the wire, the 4-french sheath is removed, and the endoluminal bypass is created in a standardized fashion.

Conclusion

The ipsilateral antegrade-retrograde approach is a fast, cheap and easy-to-learn technique, using standard materials only . The distal entry of the occlusion will lead to a minimization of the length of the endoluminal bypass, thereby possibly sparing collaterals and future surgical options.

Introduction

The endoluminal femoropopliteal bypass is slowly gaining popularity for the treatment of long chronic occlusions of the superficial femoral artery. In a randomized controlled trial, McQuade et al. have recently shown that the management of superficial femoral artery occlusive disease with percutaneous endografts has a similar primary patency at 4-years when compared to conventional femoral popliteal artery bypass grafting using a synthetic conduit[1]. Limb salvage rates were also comparable. The percutaneous technique is considered to be associated with lower morbidity compared to open bypass surgery, due to its minimal invasive character. The role of endografts in the treatment algorithm of occlusive disease in superficial femoral artery, however, remains a matter of debate. Recently, Boufi et al. observed in a retrospective study in 54 limbs that combining subintimal angioplasty with an endograft in femoropopliteal lesions did not improve patency when compared to angioplasty only[2]. These data, however, are in contrast with the observations of Saxon et al., who found in a prospective multicenter randomized study that the use of an endograft was correlated to a significantly higher technical success rate (95% vs. 66%) and 1-year primary vessel patency rate (65% vs. 40%)[3]. A patency benefit was seen for those lesions longer than 3 cm and at 12 months the chronic limb ischemia status was 15% further improved for the endograft group.

Technical failure of endovascular treatment of chronic total occlusions is most often caused by the inability to re-enter the true lumen after the occlusion is crossed in a subintimal plane. The incidence of technical failure due to the inability to re-enter the true lumen using standard catheter and wire techniques may vary between indications and centers but may be as high as 26%[4]. In case of technical failure there are various alternative approaches, including the use of re-entry devices. We describe a technique using an ipsilateral combined antegrade-retrograde approach to insert an endoluminal femoropopliteal bypass.

Surgical technique

Between January 2010 and April 2011 four patients were treated with the ipsilateral antegrade-retrograde approach to insert an endoluminal femoropopliteal bypass for

peripheral arterial disease. All were in the third category according to Rutherford and had a TASC-II D lesion. The indication for this approach was always the inability to re-enter the healthy lumen of the femoropopliteal artery using standard antegrade techniques. Preoperatively, patients received 5000 I.U. heparin and 1 gram cefazolin intravenously. In all patients the common femoral artery was punctured using ultrasound and a 6-french introducer sheath was inserted onto the superficial femoral artery. Then, the occlusion was crossed using a Terumo® wire (Terumo Medical Corporation, Elkton, MD) and a catheter. When various attempts to re-enter the true lumen had failed, an OUTBACK® LTD® re-entry device (Cordis Corporation, Bridgewater, NJ) was tried in one patient unsuccessfully. Then, the approach was converted into the ipsilateral antegrade-retrograde approach. In a supine position, the leg was elevated 30 degrees in the hip in a stable position using a sterile support. The popliteal artery was punctured in a dorsal approach using ultrasound in three patients and using fluoroscopy in combination with a roadmap in one patient and a 4-french introducer sheath was placed. Using the Terumo® guide wire the occlusion was crossed again (fig 1) and proximally the wire was advanced into and through the 6-french sheath in the common femoral artery, thereby creating a 'body floss' (fig 2). Subsequently, the occlusion was pre-dilated with an angioplasty balloon. The re-entry site was identified on an angiogram made through the 4-french sheath. Then the wire was withdrawn into the balloon catheter, leaving the 4-french introducer sheath in place, and advanced intraluminally into one of the crural vessels (fig 3). After confirming the intraluminal position of the wire, the 4-french sheath was removed, providing hemostasis using compression, and the endoluminal bypass was created in a standardized fashion using heparin-bonded ePTFE-covered stentgrafts (Viabahn®, W.L. Gore, Flagstaff, AZ, USA (Fig 4)). Angiography showed a good deployment of the endografts and outflow. In one patient an additional stentgraft had to be placed distally to cover a dissection close to the distal edge of the bypass. The 6-french sheath was removed from the common femoral artery and the puncture site was closed using a closure device (Angio-Seal™, St. Jude Medical, St. Paul, MN). There were no bleeding complications and all patients were discharged from the hospital the first postoperative day. During follow-up, varying between 1 and 7 months, all bypasses remained patent.

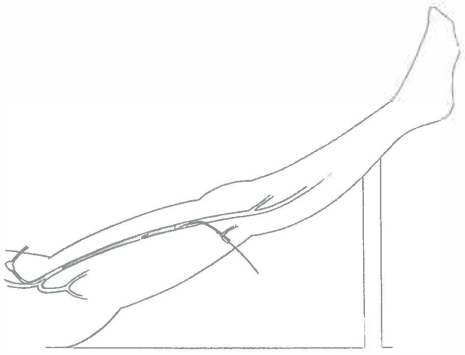

Figure 1.

The leg is elevated 30 degrees and the popliteal artery is punctured. Subsequently a 4 french introducer is placed and the occlusion is passed subintimally.

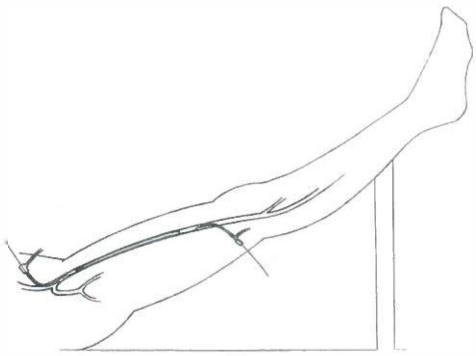

Figure 2.

The wire is extracted through the 6 french introducer sheath in the common femoral artery.

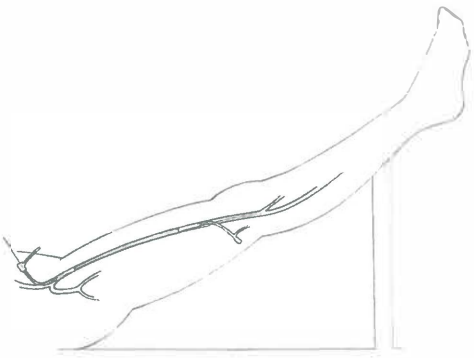

Figure 3.

Following pre-dilatation the distal end of the wire is positioned in a secure position in the crural vessels.

Discussion

In all 4 treated patients the ipsilateral antegrade-retrograde approach proved to be a fast and successful technique and no complications of the additional popliteal puncture occurred. There are multiple advantages of the combined antegrade-retrograde technique for re-entering the true lumen distal from a chronic occlusion of the superficial femoral artery. First, the technique is easy to learn and the popliteal artery may be punctured using either ultrasound or fluoroscopy using standard techniques. Second, because the occlusion is entered distally, the distal 're-entry' site will always be as proximal as possible, which will minimize the length of the endoluminal bypass. As a consequence, collaterals may be spared and in case of an occlusion of the bypass all surgical options will remain available. Third, although the use of re-entry devices, such as the Outback catheter, is related to a high procedural success of 88-96% and a low complication rate, these devices increase procedural costs[5,6]. Since in the here described technique only standard materials are used the technique is extremely cheap when compared to the use of these re-entry devices.

A retrograde transpopliteal recanalization of the superficial femoral artery has previously been described. In a series of 56 patients, in which an antegrade subintimal angioplasty could not be completed due to re-entry failure, they described a 98% success rate using a retrograde technique using a bare metal stent in 71% of cases. An inconvenience of their technique is that patients should be turned from a supine into a prone position during treatment[7]. Recently, Lesperance et al. have described a technique for the retrograde stentgraft angioplasty of a superficial femoral artery occlusion[8]. Disadvantage of this retrograde technique is the necessity to place a 6- of 7-french sheath into the popliteal artery. Therefore, they opted for an open above-knee popliteal artery exposure. Since in our technique only a 4-french introducer sheath is inserted no popliteal dissection is necessary and the technique will remain strictly percutaneous. Recently, Kawarada and Yokoi have published a case report, using a similar technique as we used in our patients[9]. They successfully treated the occluded segment using a bare metal stent that was placed in an antegrade fashion.

The role of covered stents in the treatment algorithm of occlusive superficial femoral artery disease is still a matter of dispute. During the study period, all patients in our center with a lesion length of over 10 cm were preferably treated with an endograft when

an endovascular treatment strategy was chosen. Since October 2010, these patients are included in the multicenter randomized SuperB trial (NCT01220245), comparing a heparin-bonded endograft with the current gold standard for long lesions, the venous femoropopliteal bypass.

Conclusion

The ipsilateral antegrade-retrograde approach is a fast, cheap and easy-to-learn technique. The distal entry of the occlusion will lead to a minimization of the length of the endoluminal bypass, thereby possibly sparing collaterals and surgical options.

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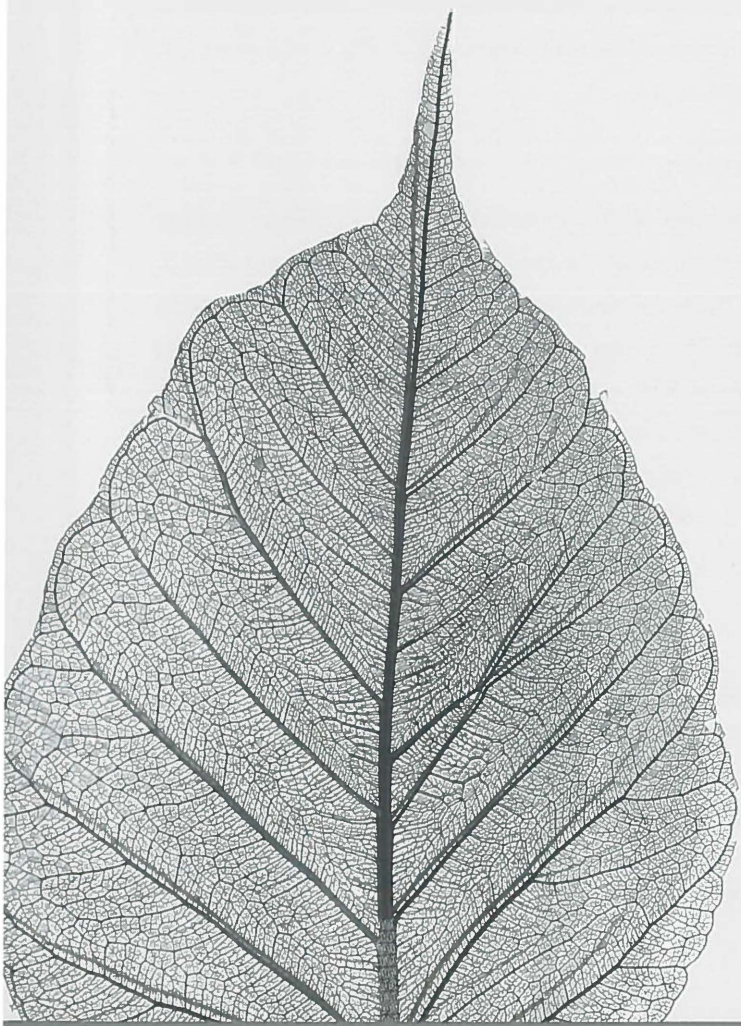
Chapter 8

SUrgical versus PERcutaneous Bypass: SUPERB-trial; heparin-bonded endoluminal versus surgical femoropopliteal bypass; a study protocol for randomized controlled trial



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Abstract

Background

Endovascular treatment options for the superficial femoral artery are evolving rapidly. For long lesions, the venous femoropopliteal bypass is considered to be superior above the prosthetic bypass. An endoluminal bypass, however, may provide equal patency rates compared to the prosthetic above knee bypass. The introduction of heparin-bonded endografts may further improve patency rates. The SUrgical versus PERcutaneous Bypass (SuperB) study is designed to assess whether a heparin bonded endoluminal bypass provides equal patency rates compared to the venous bypass and that it is associated with improved quality of life, related to a decreased complication rate, or not.

Methods/design

Two-hundred-twenty-two patients with peripheral arterial occlusive disease, category 3-6 according to Rutherford, will be randomized in two treatment arms; 1. the surgical femoropopliteal bypass, venous whenever possible, and 2. the heparin-bonded endoluminal bypass. The power analysis was based on a non-inferiority principle, with an effect size of 90% and 10% margins (alpha 5%, power 80%). Patients will be recruited from 5 teaching hospitals in the Netherlands during a 2-year period. The primary endpoint is primary patency and quality of life (evaluated by the RAND-36 questionnaire and the Walking Impairment Questionnaire). Secondary endpoints include secondary patency, freedom-from-TLR and complications.

Discussion

The SuperB trial is a multicentre randomized controlled trial designed to show non-inferiority in patency rates of the heparin-bonded endograft compared to the surgical bypass for treatment of long SFA lesions, and to prove a better quality of life using the heparin bonded-endograft compared to surgically treatment, related to a reduction in complications.

Trial registration: Clinicaltrials NCT01220245

Background

In the treatment of long lesions of the superficial femoral artery (SFA) the surgical venous bypass is considered the gold standard[1]. Bypass surgery, however, is associated with complications and a prolonged hospital length of stay. Endovascular techniques have advanced and provided new treatment options for peripheral vascular disease, but may also induce complications as was shown in the Basil trial[2]. Last few years evidence has been accumulating that the treatment of long lesions with (covered) stents may provide acceptable short- and midterm primary patency rates, as summarized in several recent reviews[3-7].

Randomized trials have shown that 1-year patency rates of self-expanding nitinol metal stents vary between 70-90% as recently summarized by Lin et al[5]. Despite improvements in stent design and introducer sizes, one of the major issues limiting patency is in stent restenosis. It was recently demonstrated that with the use of covered stents, restenosis is reduced to edge stenosis only[8]. The efficacy of an ePTFE-covered nitinol stent (Viabahn, W.L. Gore, Flagstaff, AZ, USA) in treating chronic SFA long lesions, over 8 cm in length, is currently being compared to bare nitinol stents in a multicentre randomized controlled trial (VIBRANT trial). The study hypothesis is that the use of ePTFE-covered nitinol stents will result in greater mid-term (24 months) and long-term (36 months) patency. Although interim analysis has shown no significant differences at one-year, final results have to be awaited. Recently, the 4-year results of a randomized trial have been published comparing an ePTFE-covered nitinol stent with the above-knee ePTFE femoropopliteal bypass[9]. The 1-year and 2-year patency rates were 73% and 74%, and 63% and 64%, respectively[10,11]. At 4-year follow-up, the primary patency rates were 59% and 58% respectively, and limb salvage rates were also comparable. When compared to a prosthetic bypass, however, the venous bypass has better patency rates, with 1-year and 4-year primary patency rates of 87% and 70%, respectively. There are patient groups with long lesions of the SFA, especially patients with severe co-morbidities, that might benefit from a less invasive treatment strategy. The risk of wound complications, limb edema, loss of the great saphenous vein, and cardiac complications may have to be taken into account when deciding to treat surgically or endovascularly.

Heparin-bonded prosthetic bypass grafts have shown improved patency rates in animal models and non-randomized clinical trials[12,13,14]. Recently, the heparin-bonding technology

has been integrated within the Viabahn endograft. Using this technique results may further improve to the level of the current gold standard; the venous femoropopliteal bypass. Advantages of the endoluminal technique would be related to its minimal invasive character: less pain, earlier recovery and less early complications. To date, no studies have been performed to compare the use of heparin-bonded endografts for the treatment of long lesions of the SFA. The current study has been designed to compare the use of heparin-bonded endografts for the treatment of long lesions of the SFA to the venous surgical femoro-popliteal bypass in a multicentre randomized controlled trial.

Methods and design

Study design

The design of the study is a multicentre prospective randomized controlled trial comparing the patency of the heparin-bonded endograft to the venous surgical bypass. Endpoints are primary patency after 1, 2 and 5 years, complications and quality of life.

Study objectives

The aim of the study is to demonstrate that the heparin-bonded endograft provides equal patency rates compared to the venous surgical femoropopliteal bypass. In addition we hypothesize that patients receiving a heparin-bonded endograft show better quality of life at 30-days compared to patients who were surgically treated.

Sample size calculation

The assumption has been made that the heparin-bonded endoluminal bypass will have a similar cumulative primary patency at one year compared to the autologous venous surgical bypass. For a non-inferiority trial with an effect size of 90% and a margin of 10%, 111 patients per group are needed (alpha 5%, power 80%). The effect size of 90% refers to an estimated patency rate at one year in the surgical control arm.

The assumption has been made that the heparin-bonded endoluminal bypass will have an increase in QOL, as measured by a 10-point increase in the SF-36 score, at 30 days follow-up. With a standard deviation of 20, 63 patients per group are needed (alpha 5%, power 80%).

Significance will be tested with the Student-t test (normal distribution) of Mann Whitney U-test (skewed distribution).

Setting

Patients will be recruited from the following centers: Rijnstate Hospital, Arnhem; Isala Clinics, Zwolle; Nij Smellinghe Hospital, Drachten; Antonius Hospital, Sneek; University Medical Center Groningen, Groningen, The Netherlands. In each of the participating centers, each surgeon performing the endovascular procedure must have placed at least ten endoluminal bypasses prior to treating patients who participate in the SuperB trial to prevent a learning curve bias.

The total study duration will be 7 years; the recruitment period will take 2 years and thereafter patients will be evaluated yearly until 5 years post-procedure.

Primary endpoints

The primary endpoints of the study are the primary patency at 1-year follow-up. In addition the quality of life, using the RAND SF36 Questionnaire, will be evaluated as a primary endpoint.

Secondary endpoints

1. Secondary patency
2. Complications
3. Clinical improvement
4. Surgical and endovascular re-interventions
5. Target lesion revascularization
6. Additionally an exploratory, thus hypothesis generating, subgroup-analysis will be performed.
   - Patients with disabling intermittent claudication (Rutherford 3) will be analyzed separately using pain-free and maximal walking distance and the Walking Impairment Questionnaire as additional endpoints.
   - Patients with ischemic rest pain and necrosis (Rutherford 4-6) will be analyzed using major amputations as an endpoint.

Ethical considerations

A patient who meets the entry criteria is fully informed about the trial and provided with a patient information and consent form. Patients willing to participate in the study are included after signing the informed consent form. This study is conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study is approved by the Medical Ethics committee of Nijmegen (CMO 2010-089) and the local institutional board of each participating center.

Safety and quality control

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will review safety and makes recommendations regarding the conduct of the study to the steering committee and to the accredited Medical Ethical Board (METC) that approved the study protocol. An interim safety analysis will be performed at 1-year after initiation of the trail. This analysis will include at least 40 patients.

Adverse and severe adverse events

Adverse events (AE) are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the investigational device. This definition includes events occurring during hospital stay up to 30 days of follow-up. Underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease will be reported as an AE. All AEs will be monitored from the time of enrolment through the 30-day follow-up visit. AEs will be recorded on the case record forms (CRFs). A description of the event, including the start date, end date, action taken, and the outcome will be provided.

A severe adverse event (SAE) is any event leading to death, major amputation or definitive graft failure.

Data on AEs will be reported to the DSMB and to the accredited METC via "Toetsingonline" on the website of the Central Committee on Research involving Human Subjects (CCMO, ccmo.nl).

Inclusion criteria

- Patients over 18 years of age
- Informed consent
- De novo stenosis, re-stenosis (Peak Systolic Velocity (PSV) ratio>2.5) or occlusion of the native SFA, all >10cm in length
- Popliteal artery is patent at the upper margin of the patella to the trifurcation
- Diameter of the native SFA and popliteal arteries are 5.0 to 7.5 mm
- Rutherford category 3-6
- Indication for surgical bypass
- Distal runoff at least 1 crural vessel without significant stenosis
- Resting ankle-brachial index (ABI) <0.8 in the study limb prior to procedure

Exclusion criteria

- Patient unsuitable for administration of contrast agent
- Pregnancy
- Dementia or altered mental status that would prohibit giving conscious informed consent
- Need for adjunctive major surgical or vascular procedures within 1 month
- Untreated flow-limiting aorto-iliac occlusive disease
- Unsuccessful ipsilateral percutaneous vascular procedure to treat inflow disease just prior to enrollment
- Previous ipsilateral bypass surgery or stentplacement
- Femoral or popliteal aneurysm of target vessel
- Non-atherosclerotic disease resulting in occlusion (e.g. embolism, Buerger's disease, vasculitis)
- Severe medical co morbidities (untreated coronary artery disease /congestive heart failure, severe chronic obstructive pulmonary disease, metastatic malignancies, dementia, etc.) or other medical condition that would preclude compliance with the study protocol
- Major distal amputation (above the trans metatarsal) in the study limb
- Any previously known coagulation disorder, including hypercoagulability
- Contraindication to anticoagulation or antiplatelet therapy
- Known allergies to stent or endograft components

- History of prior life-threatening reaction to contrast agent
- Patients with known hypersensitivity to heparin, including those patients who have had a previous incidence of heparin-induced thrombocytopenia (HIT) type II
- Planned surgical procedure or major amputation to occur after enrollment of the patient

Recruitment

Patients with symptomatic peripheral arterial disease of the superficial femoral artery with a Rutherford category 3-6[15] may be included in the study and will be recruited among the 5 participating centers.

Randomization

Randomization will be performed during the out patient department visit in which the patient is included. The including physician will call the telephone number provided by the principle investigator. The person answering the phone will draw an envelope from a box of plain white envelopes containing the randomization choice. The envelopes are divided in batches of 20 and randomization is stratified by center.

Imaging

All patients included in the study are screened by ultrasound imaging. Additionally, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) will be performed. These imaging studies will be performed according to the local protocol of the participating centers. The lesions in the SFA will be categorized according to the Trans Atlantic Intersociety Consensus (TASC)-II criteria. Type B, C, and D lesions may be included.

Treatment details

Endovascular technique

Antibiotic prophylaxis is administered. Preferably a percutaneous technique is used, but in case of a flush occlusion or a diseased common femoral artery, an open approach is allowed. The SFA may be approached in a contralateral retrograde or an ipsilateral antegrade fashion. When there is a concomitant lesion in the common or profunda

femoral artery an endarterectomy may be performed followed by the endoluminal bypass. Heparin (5000 I.U.) is administered. The diseased segment of the SFA is passed, either endoluminal or sub-intimal and a re-entry is created distally. The segment is pre-dilated with a regular angioplasty balloon and the endografts are positioned from distal to proximal without or with minimal oversizing. The entire diseased segment is covered with the stentgrafts and the stentgrafts are postdilated with an angioplasty balloon with the same size as the stent graft. Control angiography is performed routinely and the access is closed using a closure device, according to local protocols.

The used endograft is the heparin-bonded Viabahn Endoprothesis (W.L. Gore & associates, Flagstaff, AZ), which is a self-expanding helical nitinol stent covered with a heparin-bonded thin polytetrafluorethylene (ePTFE) tube. The size of the stentgraft should be at least 6 mm.

Post procedurally, all patients will be treated with acetylsalicylic acid 80 mg and clopidogrel 75 mg for the first year unless oral anticoagulation is indicated for other reasons. After 1 year patients may be switched to one thrombocytaggregation inhibitor. All patients receive statin treatment, started before the intervention.

Open surgical technique

The surgical femoropopliteal bypass is performed according to local protocols. Preferably the greater saphenous vein is used as conduit in all patients. The used vein has a diameter of at least 3.5 mm. Pre-operative vein mapping may be performed, but is not obligatory. When the great saphenous vein is unavailable or unsuitable a prosthetic graft may be used. When a prosthetic conduit is used the participating surgeon will explicit this choice. All patients will be included in the intention-to-treat analysis.

Post procedurally, all patients will be treated with acetylsalicylic acid 80 mg and clopidogrel 75 mg for the first year unless oral anticoagulation is indicated for other reasons. After 1 year patients may be switched to one thrombocyt aggregation inhibitor. All patients receive statin treatment, started before the intervention.

Follow-up

Follow-up is planned at 1, 3 and 6 months. Afterwards patients will be seen each 6 months until 2 years. From 2 to 5 years patients will be evaluated annually. Duplex ultrasound imaging, ankle-brachial indices, and QOL scores will be measured at all above mentioned

time points. All primary and secondary endpoint are registered as defined in the study protocol.

QOL scores

- RAND-36 is a multidimensional measurement of health. This will be used in both groups
- WIQ (Walking Impairment Questionnaire) is especially designed for patients with claudication, and will only be used in patients treated for claudication.

These scores are taken prior to the intervention and at defined times afterwards (i.e. 1 day, 1 week, 1 month, etc).

Data collection

Data will be collected at the recruitment centre by means of case report forms (CRF's). The copies of the CRF forms will be sent to the coordinating center (Rijnstate Hospital) where all data will be entered in the central database and controlled by an independent monitor. The participating centers will be informed about the current status of recruitment and adverse events via a newsletter every 3 months. Additionally, there will be regular contact between the principle investigator and the contact persons from the participating centers.

Statistical analyses

Data concerning the 1, 2 and 5 year follow-up will be analyzed for both study groups in an intention-to-treat and a per-protocol manner by student t-test (normal distribution) of Mann Whitney U-test (skewed distribution). Corrections will be made for study centre. Additionally, in case of sufficient numbers, the data will be analyzed for different TASC II categories; otherwise the analyses will be additionally adjusted for TASC II categories. Patency rates will be presented as Kaplan Meier curves including censoring.

Publication of data

Data will be published after a follow-up period of 1, 2 and 5 years, regardless of the outcome of the study under the responsibility of dr. MMPJ Reijnen. Co-authorship will be assigned according to the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication' of the International Committee of Medical Journal Editors.

Definitions

- Procedural success:
  - Endovascular – Successful vascular access, exact deployment of the device and completion of the endovascular procedure and immediate morphological effect (< 30% residual stenosis)
  - Surgical – Successful access, completion of surgical procedure and clinically assessed immediate improvement
- Primary patency: The absence of occlusion or flow-limiting stenosis (PSV ratio >2.5) of the treated segment of the artery including 1 cm proximal and distal of the anastomosis, as documented by accepted imaging techniques, particularly arteriography or duplex ultrasonography, or direct observation at operation or postmortem.
- Primary assisted patency: When a secondary endovascular or open procedure is performed to prevent failure, i.e. in a flow reducing stenosis (PSV ratio >2.5), in a still-patent segment of the stent graft or bypass, including the anastomoses.
- Secondary patency: When a thrombolytic or surgical treatment has been performed for graft or stent graft occlusion in an afterwards patent vessel.
- Target lesion revascularization: Repeat percutaneous or surgical revascularization driven by clinical state in the presence of a flow reducing stenosis or occlusion in the treated segment of the artery including 1 cm proximal and distal of the anastomosis.
- Type B lesion SFA according to TASC II criteria:
  - Multiple lesions (stenosis or occlusions), each ≤ 5 cm
  - Single stenosis or occlusions ≤ 15 cm (not involving infragenuale popliteal segment)
  - Heavily calcified occlusion ≤ 5 cm in length
  - Single popliteal stenosis
- Type C lesion SFA according to TASC II criteria:
  - Multiple stenosis or occlusions totaling >15 cm with or without heavy calcification
  - Recurrent stenosis or occlusions that need treatment after 2 endovascular interventions
- Type D lesion SFA according to TASC II criteria:
  - Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
  - Chronic total occlusions of popliteal artery and proximal trifurcation arteries
- Minor amputation: Below the ankle amputation, planned or unplanned.

- Major amputation: Above the ankle amputation, planned or unplanned
- Clinical improvement: Improved Rutherford classification compared to baseline.
- Intermediate lesion: Occlusion or stenosis > 10 cm length
- Flow-reducing (re-)stenosis: A stenosis with a PSV ratio of more than 2.5 as measured by duplex, or a >50% (re-)stenosis on angiography, MRA or CTA.
- Graft failure: Definitive occlusion of the bypass with unsuccessful thrombolytic or surgical treatment
- Re-intervention: Secondary percutaneous or surgical intervention of the bypass.
- Seroma: Non-infected fluid accumulation under the wound
- Hematoma: Accumulation of blood postoperatively in the operated area.
- Re-bleed: Accumulation of blood postoperatively requiring operative treatment.
- Abscess: Accumulation of pus in the operated area.
- Infected wound: Red, swollen, but closed wound, not requiring surgical drainage.
- Open wound: Non infected wound leaking fluid.
- Loss of sensibility: Postoperative clinical loss of sensibility of the skin in the operated leg.
- Femoral nerve damage: Clinical femoral nerve damage.
- Graft infection: Proven graft infection requiring long term use of antibiotics or graft removal.
- Edema: Postoperative persistent edema of the operated leg.
- Serious adverse event (SAE): An adverse event that leads to death or serious deterioration in the health of the subject, defined as death, definite failure of graft/ bypass or major amputation in the treated leg

Discussion

The aim of the present randomized trial is two-fold. First, it aims to compare patency rates of the endoluminal bypass, combined with the heparin-bonded technology, with the current gold standard, the venous femoropopliteal bypass, the current gold standard. Second, it aims to demonstrate that an endovascular approach is associated with fewer complications and thus an improved quality of life. In order to have sufficient power, the trial was designed using a non-inferiority principle.

Data analysis will be performed in both an intention-to-treat as a per-protocol manner. The first will be performed to compare the endoluminal bypass with common surgical practice, namely that some patients will not have a vein usable for the bypass and that some endoluminal procedures will be converted to open surgery. The per-protocol analysis will give information about the performance of the endoluminal bypass itself.

There are several differences between the SuperB trial and previously published randomized trials[9,16]. The SuperB trial is the first trial using a heparin-bonded endograft and the inclusion criteria are chosen much broader since hybrid procedures, such as a reconstruction of the common femoral artery, are allowed. Moreover, the anti-platelet regime and the use of statins are standardized. The wide inclusion criteria are chosen because they mimic common surgical practice and thereby they reduce the risk on inclusion problems as was the case in the Scandinavian trial[16].

With the introduction of the heparin-bonded technology in the endograft the design of the stent has also been changed. The proximal edge of the endograft has no longer a straight, but a contoured edge. This adaptation will reduce infolding in case of oversizing, thereby maintaining laminar blood flow and preventing intimal hyperplasia and thus edges stenosis. The expected effect of the new endograft may therefore not only be attributed heparin-bonding technology.

The SuperB trial hypothesizes that the treatment of the long lesion of the SFA with a heparin-bonded endograft will show equal patency rates compared to the surgical bypass, but a better quality of life for treatment with the heparin-bonded endograft is expected, related to a reduced morbidity. Therefore, patients will be asked to fill out the RAND 36 questionnaire before treatment and at each visit during follow-up. Patients with intermittent claudication additionally will be asked to fill out the Walking Impairment Questionnaire at the same visits. Trials on endoluminal bypass including quality of life scores have not been performed, to date.

In conclusion, the SuperB trial is a multicentre randomized controlled trial designed to show equality in patency rates of the heparin-bonded endograft compared to the surgical bypass for treatment of longer lesions of the SFA, but to show better quality of life using the heparin bonded-endograft compared to surgically treatment, related to a reduction in complications.

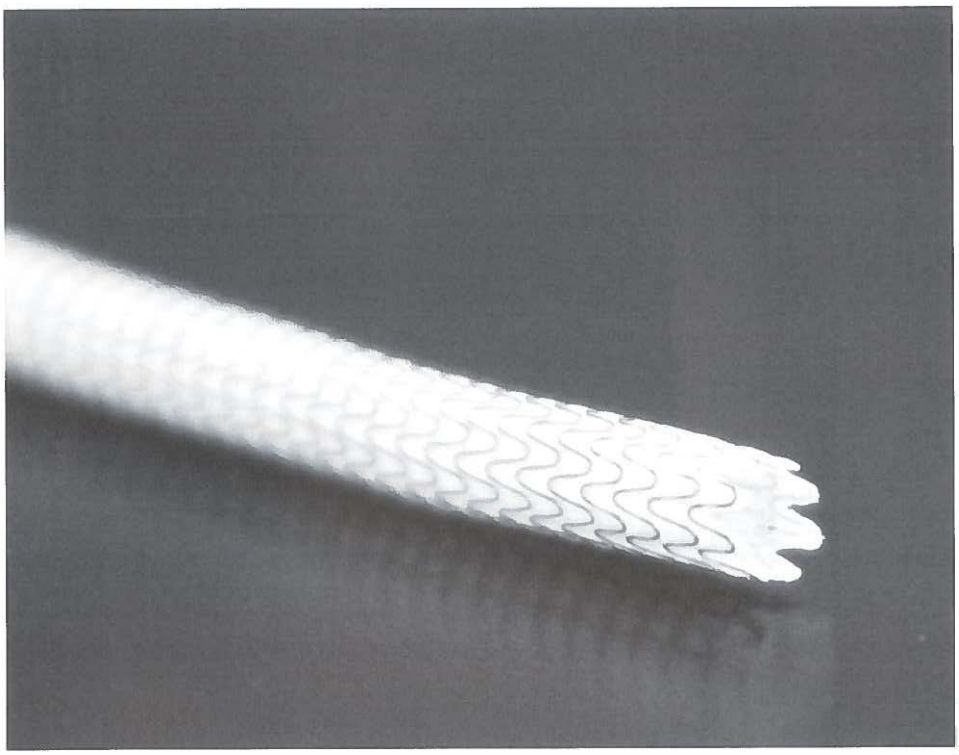

Figure 1. The Viabahn endograft (W.L. Gore, Flagstaff, AZ, USA) with a contoured proximal edge.

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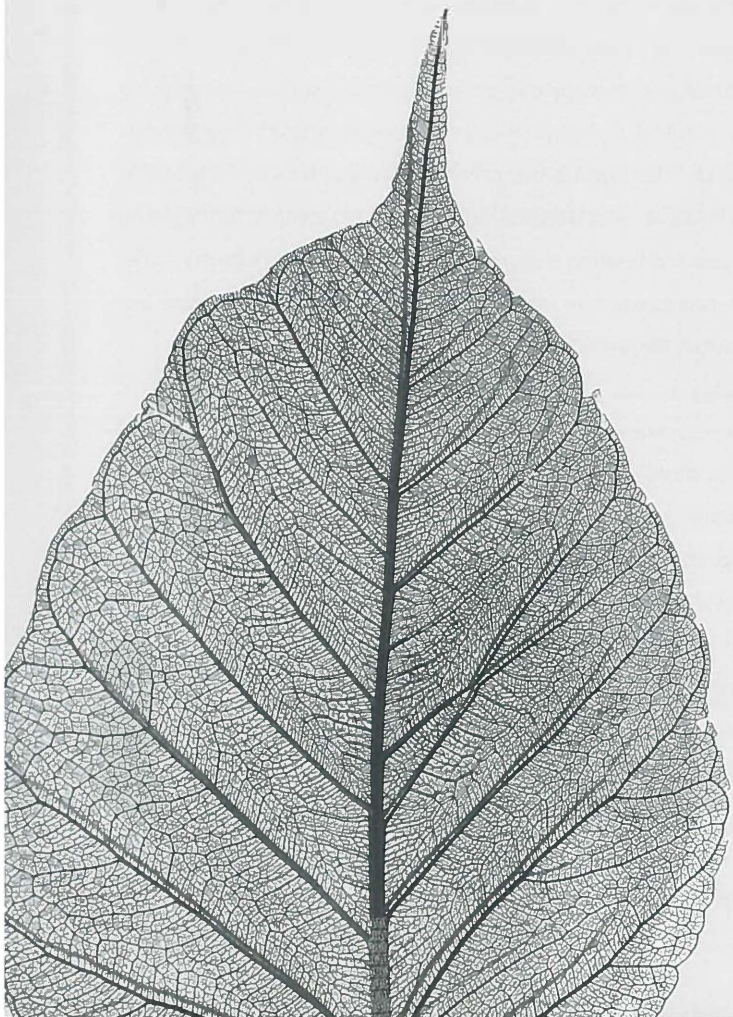
Chapter 9

Summary and general discussion



General discussion

Since the development of the venous femoropopliteal bypass by Kunlin in 1948, it has been the standard treatment modality for long lesions of the superficial femoral artery (SFA)[1]. Recent technical advances made endoluminal techniques feasible after which the endograft treatment modality was added to to the treatment algorithm of chronic occlusive disease. In the previous chapters we tried to define the exact role of this relatively new treatment modality.

It goes without saying that the primary treatment of peripheral arterial disease (PAD) consists of best medical treatment[2,3]. Antiplatelet and statin therapy are started at the onset of symptoms. Specifically patients who present with intermittent claudication (IC) gain advantage with exercise, i.e. supervised walking training[4,5,6]. In patients with chronic Rutherford category 3-6 surgical therapy can be considered if supervised walking training fails. When opting for surgical therapy, in case of longer lesions, the venous bypass is still the golden standard[7]. This bypass has primary patency rates of 75% at five years[8,9]. Surgical reconstruction however is related to high morbidity rates, including early postoperative complications as wound healing disturbances (5-44%)[7,10] and edema (40%-100%)[11,12]. Surgical bypass is related to a failure rate of 10% to 20% at one-year follow-up, for a venous and prosthetic conduit, respectively[13].

Endoluminal techniques can play a role in both primary and secondary procedures *(Chapter 2, Chapter 6)*. Percutaneous transluminal angioplasty (PTA) is already considered the treatment of first choice with short lesions of the SFA[1]. When treating longer lesions of the SFA (>10cm) endoluminally, stenting is recommended[14,15,16]. To prevent in stent restenosis due to neointimal hyperplasia after endoluminal therapy in TASC-II C/D lesions, these are preferably treated with a covered nitinol stent. Covered stents reduce restenosis to edge stenosis alone[17], which is easier to treat than in stent restenosis. Several studies describe improved primary patency rates from 70%[14,15,16] to 83%[18,19] with covered nitinol stent placement. Patency rates of non heparine-bonded endografts are comparable with those of synthetic bypasses (two-year primary 63% vs 64% for bypass[20]).

An endoluminal bypass offers several advantages. It is a minimal invasive alternative in the often frail vascular population. No major surgery is necessary. Endoluminal stentgrafts can be placed either percutaneously or with an inguinal incision. This procedure can be performed under local anesthesia. The minimal invasive character translates to a lower

complication rate. As described in chapter 3 our overall complication rate was 7.5%. In our series no patients developed wound healing problems and only one developed postoperative edema. Another advantage of an endograft is the earlier postoperative recovery. After a venous bypass, patients are admitted an average of 5 days postoperatively (4.4-9.1 days[21,22]). Our patients were admitted for less than three days and there were no intensive care unit admissions after endograft placement *(Chapter 3)*.

Primary use of an endoluminal bypass evades surgical bypass surgery in 89% of patients through patency or clinical improvement despite failure of the endograft (at 2-year follow-up, *Chapter 4*). And if an endograft fails, secondary surgical bypasses remain possible, with potentially the greater saphenous vein available as the endoluminal bypass preserves the autologous vein. Collateral loss after endograft placement has always been considered a disadvantage of the technique. The overstenting of collaterals might worsen the clinical state of patients after failure of the endograft. In Chapter 4 and 5 we describe the outcome of patients after failure of the endograft. In our study population the majority of patients returned to a similar or better clinical state after failure of the endoluminal bypass (43% improved, 37% equal Rutherford category). Limb salvage rates are excellent (94-100%) and secondary surgical procedures remain possible. This confirms the observation of McQuade et al[20], that the use of covered stents in SFA occlusive disease is not related to an increased amputation rate, due to the covering of collaterals, in case of failure. These results are also supported by Doomernik et al[23]. Chapter 4 reveals that popliteal anatomy deteriorates after endograft failure. Still despite this, 75% of the patients needing secondary surgery could be treated with a AK bypass. Patency rates of these secondary procedures are 55% at 1 year. However, almost 25% of patients with a failed endograft could be treated conservatively and elude a surgical bypass completely. Endograft placement can therefore safely be seen as a bridge to surgery.

In Chapter 6 two case reports show that after failure of a primary surgical bypass an endoluminal bypass can also be considered as a secondary procedure. Most important for the success of this procedure is a non hostile anatomy. Popliteal diameter and crural outflow vessels should be of good quality. Major advantage of an endograft as secondary procedure is prevention of redo surgery, which is associated with higher morbidity rates[24-28].

Future perspectives

In the near future, long term patency rates, two years and up, of the first heparin-bonded endografts will follow. Most interesting will be to see if the endograft can match the excellent four year patency rates of the venous bypass. Primary patency rates might possibly be lower than that of the autologous venous bypass, as endoluminal techniques usually require more re-interventions to prolong patency. The number of re-interventions needed for maintaining endograft patency will be of the utmost importance as this will in part define the role of endografts in the future.

Our group is currently describing a cost analysis comparing endografts with surgical bypass. On a background of increasing costs for health care, we believe a realistic comparison of the costs is necessary. Although placement of an endograft is more expensive than placement of a venous surgical bypass, our theory is that the shorter hospital admittance, lower complication rate and possibly shorter operating theatre time will compensate for the price of the endograft. Primarily we are evaluating short term (<30 day) costs, but in the future we will expand to long term cost comparison. In this comparison the number of re-interventions needed for endograft patency will be evaluated as this is usually seen as a major cost factor. In our series, as described in Chapter 3, only 4 (7.1%) PTA's (2 with stent placement) were necessary in 56 treated limbs to prevent failure. So perhaps long term costs of the endograft will also be comparable to those of the surgical bypass.

In recent studies describing results of the endograft one-year primary patency rates varied between 44% and 95%[29,30]. The antithrombogenic strategy, among other things, greatly differed between these studies. In most series patients were treated with acetylsalicylic acid while in half of them clopidogrel was added for 6 weeks to over 3 months. In a study focusing on patients with a popliteal artery aneurysm, treated with an endograft, it was shown that the use of clopidogrel was the only predictor for outcome[31] emphasizing the importance of proper medical treatment. Based on this series, and extrapolated from the DES in cardiology we treat our patients with clopidogrel for one year. Future studies should further describe best medical treatment after placement of endografts.

In synthetic surgical bypasses heparin bonding improved patency rates to the level of the venous bypass (69-81% at two years). Recent developments have combined the technique of heparin bonding with endografts. These developments could increase patency rates. We commenced a prospective randomized controlled trial, the SUrgical versus PERcutaneous Bypass (SuperB, NCT01220245) as described in Chapter 8. The

aim of this randomized trial is two-fold. First, it compares patency rates of the endograft with the current gold standard, the venous femoropopliteal bypass. Secondly, it aims to demonstrate that an endovascular approach is associated with fewer complications and thus an improved quality of life. We believe that within the frail vascular population this QoL is important. Our SuperB trial hypothesizes that the treatment of long lesions of the SFA with a heparin-bonded endograft will show comparable patency rates compared to the surgical bypass, but a better quality of life, related to reduced morbidity.
It would also be interesting to compare endograft placement to other minimal invasive procedures, such as the remote endarterectomy. Comparative studies such as these, assessing both patency and quality of life, are essential in defining the role of heparin-covered stent-grafts in the treatment algorithm of chronic occlusive SFA disease.

General conclusion

Based on our studies we have shown that the use of heparin-bonded covered stents for long chronic occlusions of the SFA is feasible, safe and approaches patency rates within the range of surgical venous reconstruction. This indicates that the use of heparin-bonded stent-grafts might be a viable alternative for surgery in a specific group of patients.

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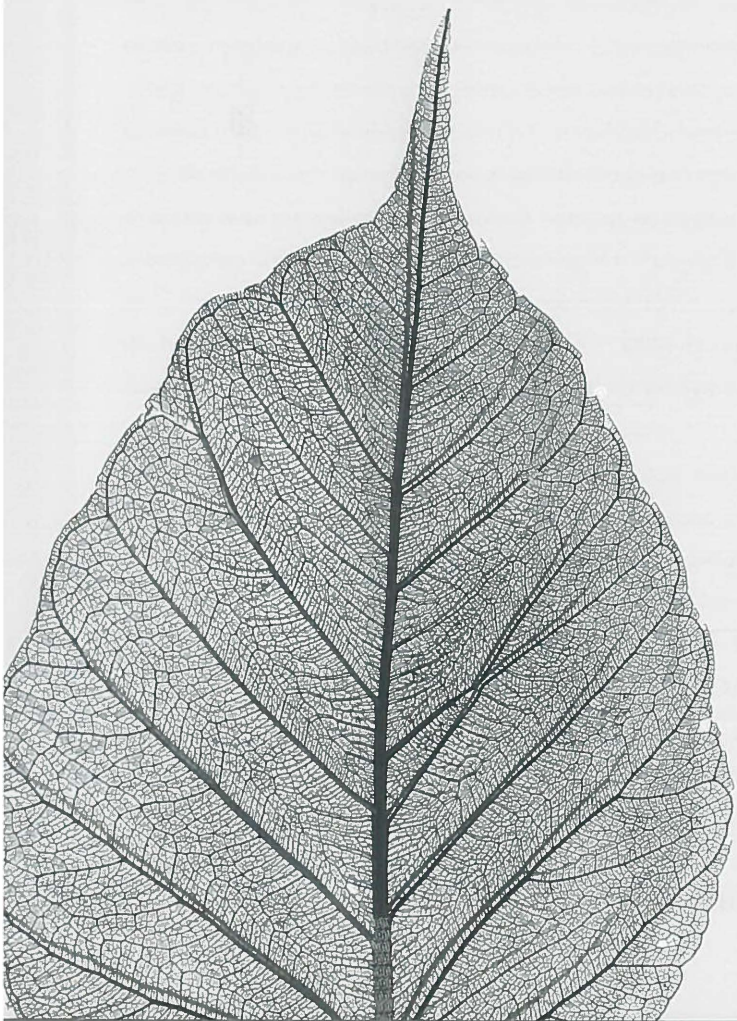
Chapter 10

Nederlandse samenvatting en discussie



Algemene discussie

Sinds de ontdekking van de veneuze femoropopliteale bypass door Jean Kunlin in 1948, is het de gouden standaard voor lange vernauwende afwijkingen van de arteria femoralis superficialis (AFS)[1]. Recente technologische ontwikkelingen hebben de endoluminale technieken toegevoegd aan het scala aan behandelopties voor chronisch oblitererend perifeer vaatlijden. In de vorige hoofdstukken hebben we geprobeerd de precieze rol van deze relatief nieuwe behandelmodaliteit te omschrijven.

Natuurlijk bestaat de primaire behandeling van perifeer vaatlijden uit optimale medicamenteuze behandeling[2,3]. Thrombocytenaggregatieremmers and statines dienen vanaf de eerste presentatie van symptomen gestart te worden. Patiënten die zich presenteren met claudicatio intermittens (CI) hebben bewezen baat bij gesuperviseerde looptraining[4-6]. Wanneer deze conservatieve behandeling onvoldoende resultaat geeft, kan er bij patiënten met Rutherford classificatie 3 t/m 6 besloten worden tot operatief ingrijpen. Bij de keuze tot chirurgische behandeling is voor lange laesies van de AFS de autologe veneuze bypass nog steeds de gouden standaard[7]. Deze bypass kent primaire patencies van 75% na vijf jaar follow-up[8,9]. Helaas is chirurgische reconstructie gerelateerd aan een hoge kans op morbiditeit, in het bijzonder op vroege postoperatieve complicaties zoals wondgenezingsstoornissen (5-44%)[9,10] en oedeem (40-100%)[11,12]. Uiteindelijk faalt 10 tot 20% van de chirurgische bypass binnen 1 jaar[13] (respectievelijk autoloog veneus en kunststof bypass).

Endoluminale technieken kunnen een rol spelen in zowel de primaire behandeling van perifeer vaatlijden als de secundaire behandeling (*Hoofdstuk 2, Hoofdstuk 6*). Percutane transluminale angioplastiek (PTA) is voor korte laesies van de AFS reeds de eerste behandeloptie[1]. Bij endoluminale behandeling van lange laesies van de AFS (>10cm) wordt het plaatsen van een stent aanbevolen[14-16]. Om in-stent re-stenosen, door neo-intima hyperplasie, bij TASC-II C/D laesies te voorkomen, worden deze bij voorkeur behandeld met een gecoverde nitinol stent. Gecoverde stents beperken het voorkomen van re-stenosen tot rand-stenosen[17], welke makkelijker te behandelen zijn. Verscheidene studies beschrijven een verbetering van patency van 70%[14-16] naar 83%[18,19] bij gebruik van gecoverde stents. De niet heparine-gebonden endografts hebben primaire patencies die vergelijkbaar zijn met die van de kunststof chirurgische bypass (2-jaar primaire patency 63% vs 64% voor de bypass[20]).

De keuze vooreen endoluminale bypass heeft verschillende voordelen. Het is een minimaal invasieve behandeloptie in een vaak kwetsbare populatie. Er is geen grote chirurgie voor noodzakelijk. Endografts kunnen percutaan geplaatst worden of via een kleine inguinale incisie. Deze ingreep kan onder lokale anesthesie gebeuren. Het minimaal invasieve karakter van de endograft plaatsing vertaalt zich in een lage morbiditeit. Zoals beschreven in hoofdstuk 3, was onze algemene complicatie risico 7.5%. In onze patiëntenpopulatie waren er geen wondgenezingsstoornissen en slechts 1 patiënt ontwikkelde postoperatief oedeem. Een ander voordeel van de endograft is het snelle postoperatieve herstel. Na een autologe veneuze femoropopliteale bypass zijn patiënten gemiddeld 5 dagen opgenomen (4.4-9.1 dagen[21,22]). Onze patiënten waren gemiddeld minder dan 3 dagen opgenomen en er waren geen opnamedagen op de intensive care (*Hoofdstuk 3*).

Primair kiezen voor het plaatsen van een endograft voorkomt chirurgische interventies in 89% van de totale patiëntenpopulatie, door of patency van de endograft, of klinische verbetering ondanks falen van de endograft (na 2 jaar follow-up, *Hoofdstuk 4*). En mocht er na falen van de endograft een indicatie zijn tot behandeling dan is het secundair plaatsen van een autologe veneuze bypass nog mogelijk, omdat de endograft de eventueel aanwezige vena saphena magna (VSM) behoudt.

Hetverliesvan collateralen wordtvaak gezien als nadeel van het plaatsenvan een gecoverde stent. Het overstenten van collateralen zou de kliniek van de patiënt verslechteren, wanneer de stent occludeerd. In hoofdstuk 4 en 5 beschrijven wij de klinische uitkomst van patiënten na occluderen van de endograft. In onze populatie keerden de meerderheid van de patiënten, na falen van de endograft, terug naar hun oude of een verbeterde niveau (43% verbeterde Rutherford classificatie, 37% gelijke Rutherford classificatie). De kans op amputatie na falen was zeer klein (0-6%) en secundaire chirurgische ingrepen bleven mogelijk. Deze cijfers bevestigen de observaties zoals beschreven door McQuade et al[22], dat het gebruik van gecoverde stents niet leidt tot een hoger amputatie risico na falen van de stent. Ook Doomernik et al[23] onderschrijven onze resultaten.

In hoofdstuk 4 laten we zien dat de anatomie van de arteria poplitea (AP) verslechterd na falen van de endograft. Ondanks deze observatie kon 75% van de patiënten behandeld worden met een supragenuale bypass. De patency voor deze secundaire procedures was 55% na 1 jaar. Daarentegen kan een kwart van de patiënten na falen van de endograft conservatief behandeld worden en zo chirurgie volledig omzeilen. Het plaatsen van een endograft kan daarom gezien worden als een brug naar chirurgie.

In hoofdstuk 6 laten twee case reports zien dat na falen van een primair chirurgische bypass, een endoluminale bypass ook als secundaire behandeling gebruikt kan worden. De belangrijkste voorwaarde voor het succes van deze ingreep is een geschikte anatomie. De diameter van de AP en de crurale vaten dienen van goede kwaliteit te zijn. Het grootste voordeel van een endograft als secundaire procedure is het voorkomen van redo-chirurgie, welke geassocieerd is met hoge morbiditeit[24-28].

Toekomstperspectieven

Binnenkort zullen de lange termijns resultaten (meer dan 2 jaar) van de eerste heparine-gebonden endografts volgen. Het zal interessant zijn om te zien of deze vergelijkbare patencies heeft met de zeer goede 4-jaars resultaten van de veneuze bypass. De primaire patency zou lager kunnen uitkomen dan die van de autologe veneuze bypass, aangezien voor endoluminale technieken vaak meer re-interventies noodzakelijk zijn om de patency te behouden. Het aantal re-interventies dat noodzakelijk is zal zeer belangrijk zijn om de rol van endografts te bepalen.

Op dit moment voeren wij een kosten analyse uit waarbij we het gebruik van de endograft vergelijken met de chirurgische bypass. Met de toenemende kosten in de gezondheidszorg vinden wij een realistische vergelijking van de kosten belangrijk. Hoewel het plaatsen van een endograft duurder is dan het plaatsen van een veneuze bypass, verwachten wij dat de kortere opnameduur, het lagere aantal complicaties en de kortere operatieduur compenseren voor de kosten van de stent. Primair zullen we ons focussen op de korte termijn kosten (<30 dagen), maar in de toekomst zullen we ook de langere termijn kosten vergelijken. Ook hier zal het aantal re-interventies weer van belang zijn, aangezien dat vaak gezien wordt als grote kosten factor. In onze serie, zoals beschreven in hoofdstuk 3, waren er maar 4 PTA's noodzakelijk (7.1%) om 56 endografts patent te houden. Dus ook op de lange termijn kunnen de kosten vergelijkbaar zijn met die van een chirurgische bypass.

In recente studies varieerde de primaire patency van de endograft tussen de 44% en 95%[29,30]. Er was tussen deze studies een grote variatie in, onder andere, de gebruikte postoperatieve medicamenteuze therapie. In de meeste series werden patiënten postoperatief behandeld met acetylsalicylzuur, in de helft van de gevallen gecombineerd met clopidogrel (gedurende 6 weken tot 3 maanden). In een studie aangaande patiënten die behandeld waren met een endograft voor een popliteaal aneurysma, was het gebruik

van clopidogrel de enige variabele met een positief voorspellende waarde voor een goede uitkomst[31]. Hiermee werd de noodzaak tot goede medicamenteuze behandeling nogmaals onderstreept. Gebaseerd op deze serie, en ge-extrapoleerd van de drug-eluting stents (DES) vanuit de cardiologie, behandelen wij onze patiënten met clopidogrel gedurende 1 jaar. Toekomstige studies zullen de optimale medicamenteuze therapie na endograft plaatsing moeten onderzoeken.

In kunststof chirurgische bypasses heeft de introductie van heparine-binding de patency verbeterd tot het niveau van de veneuze bypass (69-81% na 2 jaar). Recente ontwikkelingen hebben de techniek van de heparine-binding gecombineerd met de endografts. Deze ontwikkelingen kunnen de patency van endograft mogelijk ook verbeteren. Daarom hebben wij een prospectieve, gerandomiseerde studie opgezet, de 'SUrgical versus PERcutaneous Bypass' (SuperB, NCT01220245), zoals beschreven in hoofdstuk 8. Het doel van deze gerandomiseerde trial is tweeledig. Allereerst zullen we de patency vergelijken van de endograft en de huidige gouden standaard, de autologe veneuze femoropopliteale bypass. Ten tweede willen we aantonen dat een endoluminale bypass geassocieerd is met minder complicaties en een betere kwaliteit van leven (QoL). We vinden dat in de kwetsbare vaatpopulatie deze QoL belangrijk is. De hypothese van onze SuperB trial is dat de behandeling van lange laesies van de AFS middels een endograft leidt tot een vergelijkbare patency als die van de chirurgische bypass, maar met een betere kwaliteit van leven, gerelateerd aan minder complicaties.

Het zou ook interessant zijn om de endograft te vergelijken met andere minimaal invasieve technieken zoals de remote endarterectomy (REA). Vergelijkende studies, zoals de SuperB trial, die zowel patency als QoL beschrijven, zijn noodzakelijk om de rol van heparine-gebonden endografts in de behandeling van chronisch perifeer vaatlijden van de AFS, te bepalen.

Algemene conclusie

Gebaseerd op onze studies hebben we laten zien dat het gebruik van heparine-gebonden endografts voor lange laesies van de AFS een haalbare en veilige behandeloptie is, met patencies die die van de veneuze bypass benaderen. Dit kan betekenen dat het gebruik van een heparine-gebonden endograft een goed alternatief is voor chirurgie in een specifieke patiëntenpopulatie.

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Curriculum Vitae

Curriculum Vitae

Mare M.A. Lensvelt was born on the 20th of December 1979 in Berkel Enschot, the Netherlands. In 1998 she graduated from the Cobbenhagen College in Tilburg (Atheneum). She started her medical studies in Nijmegen, at the Radboud University. During her residency she spend six months in Rubya Hospital in Tanzania.

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